Environmental Pollution 184 (2014) 354–359

Contents lists available at ScienceDirect

Environmental Pollution

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

Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation

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ARTICLE INFO

Article history:
Received 30 May 2013
Received in revised form
27 August 2013
Accepted 8 September 2013

Keywords:
Pharmaceuticals
Risk
Wastewater
Aquatic
Drinking water

ABSTRACT

We measured concentrations of 56 active pharmaceutical ingredients (APIs) in effluent samples from 50 large wastewater treatment plants across the US. Hydrochlorothiazide was found in every sample. Metoprolol, atenolol, and carbamazepine were found in over 90% of the samples. Valsartan had the highest concentration (5300 ng/L), and also had the highest average concentration (1600 ng/L) across all 50 samples. Estimates of potential risks to healthy human adults were greatest for six anti-hypertensive APIs (lisinopril, hydrochlorothiazide, valsartan, atenolol, enalaprilat, and metoprolol), but nevertheless suggest risks of exposure to individual APIs as well as their mixtures are generally very low. Estimates of potential risks to aquatic life were also low for most APIs, but suggest more detailed study of potential ecological impacts from four analytes (sertraline, propranolol, desmethylsertraline, and valsartan).

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1. Introduction

Active pharmaceutical ingredients (APIs) have been frequently detected in surface waters of developed nations (Halling-Sorensen et al., 1998), raising concerns about potential risks to humans and the environment (Daughton and Ternes, 1999). The primary route of APIs into surface waters is believed to be excretion by patients into wastewater collection systems, survival of wastewater treatment, and subsequent introduction into the aquatic environment as a component of the treated wastewater flow (Fent et al., 2006).

Estimating risks from APIs requires characterizing their environmental occurrence, but this is complicated by the number and variety of APIs in common use: over 1000 APIs are approved for use in the US (U. S. Food and Drug Administration, 2009), but most studies examining environmental occurrence only report concentrations of a handful of analytes. Differences in analytical methods and reporting formats have limited the potential of combining individual studies to generate a more complete picture of API occurrence. Furthermore, little or no measured concentration data are available for a number of widely prescribed APIs (Kostich et al., 2010).

In order to efficiently explore potential risks from this broad class of contaminants, our group conducted a preliminary risk assessment of human prescription pharmaceuticals available in the US to identify a manageable subset with the highest estimated potential for environmental impact (Kostich and Lazorchak, 2008). We then developed an analytical method targeting these priority APIs (Batt et al., 2008). Here we report the measured concentrations of 56 APIs and 7 API metabolites in effluent samples from fifty very large (15–660 MGD) wastewater treatment plants (WWTPs) located across the US. We use these results, in combination with a previously described risk assessment approach and summary of published occurrence data (Kostich et al., 2010), to draw tentative conclusions about risks from aquatic exposure for all human prescription pharmaceuticals, including those that have never been surveyed.

2. Materials and methods

2.1. Plant selection

The Clean Watershed Needs Survey (CWNS; U. S. Environmental Protection Agency, 2004) lists the size of the population served and the flow rate for most WWTPs in the US, as reported by plant operators. The survey includes data on 22,795 WWTPs with discharges, including 13,819 WWTPs that discharge into

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0269-7491/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.envpol.2013.09.013

surface waters (which does not include ocean discharge). WWTPs listed in CWNS were incorporated into our selection process if they discharged to surface water, served a population greater than 100 people, had at least 75% of their flow originating from municipal (as opposed to industrial or storm water) sources, served a population consisting of at least 75% local residents, and reported per capita wastewater production between 50 and 1000 L per person per day. This process produced a subset of 11,040 WWTPs. The largest (based on daily flow rate) 50 plants meeting the criteria were selected for the present survey. Five of these plants declined to participate. The next five largest plants, ordered by flow-rate, were selected to take their place. In aggregate, the 50 plants we sampled serve over 46 million people and discharge a total of 6.0 billion GPD (22.7 million m^3), or about 17% of all the wastewater produced by WWTPs in the US. These WWTPs are located in 20 out of 50 US States, and 8 out of 10 US Environmental Protection Agency (EPA) Regions (U. S. Environmental Protection Agency, 2013). Regions 1 and 10 did not have WWTPs included in the sample.

2.2. Effluent sample collection

Effluent samples were collected between January 11th and April 5th, 2011. Sample collection containers (1 L, amber glass) were washed in hot water with Alconox, rinsed in hot water, rinsed three times with distilled water, rinsed three times with acetone, and then baked in a heated oven at 250 °C for a minimum of four hours. A 24-h composite sample (500 mL of effluent) was collected by WWTP operators from each WWTP, using their own equipment, and 2 mL of a solution containing 5.0 g/L of Na_2EDTA and 25 mg/L of ascorbic acid was added at the time of collection. The samples were shipped overnight on wet ice, and stored at 4 °C until extraction.

Because of the large number of sampling sites and chemical analytes, it was logistically too difficult and expensive to collect and analyze field blanks as well as duplicates from each location. Field blanks were collected from 20% of the sampling sites, with the field blanks being prepared from laboratory distilled water that was transferred into sampling containers and preserved at the time of collection. Duplicates were collected and analyzed for 10% of the sample sites.

2.3. Sample preparation and analysis

Effluent samples were extracted and analyzed using two previously reported methods (Batt and Aga, 2005; Batt et al., 2008). All samples were extracted within two days of collection and extracts were stored in silanized glass vials at −10 °C until analysis. A laboratory blank consisting of distilled water, a spiked distilled water control sample, and a matrix spike control sample were also included in each extraction batch along with the wastewater effluent samples. Five hundred milliliters of each sample was filtered through a 0.7 μm filter and then spiked with respective isotopically labeled procedural internal standards (at a concentration of 1 μg/L) prior to extraction.

For Method 1 (Batt et al., 2008) analytes (see Supplemental File 1), samples were extracted with 150 mg Oasis HLB MCX cartridges at an unadjusted pH. Acidic and neutral analytes were eluted by acetonitrile and basic analytes were eluted by 95% acetonitrile and 5% ammonium hydroxide into separate silanized glass tubes. The extracts were then concentrated to dryness under a constant flow of nitrogen at 40 °C prior to reconstitution. Reconstituted extracts were transferred to polypropylene vials for immediate liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis. Extracts were analyzed for 54 APIs using a Waters Aquity ultra performance liquid chromatograph coupled to a Micromass Quattro Micro triple-quadrupole mass spectrometer with an electrospray ionization source operated using multiple reaction monitoring (MRM). Analytes were separated on a BEH C18 column (1.0 × 100 mm 1.7 μm) equipped with 0.2 μm inline filter. Four separate injections were used to cover the range of analytes, in accordance with LC–MS/MS conditions described in Batt et al. (2008).

For Method 2 analytes (Supplemental File 1), a previously reported method (Batt and Aga, 2005) was adapted for the analysis of human and veterinary antibiotics. Sample pH was adjusted to between 2.8 and 3.0 using a dilute solution of hydrochloric acid. Samples were extracted with 200 mg Oasis HLB cartridges and collected in silanized glass vials with a single elution using acetonitrile. The extracts were then concentrated to dryness under a constant flow of nitrogen at 40 °C, and reconstituted in 20% acetonitrile. Reconstituted extracts were then transferred to polypropylene vials for immediate LC–MS/MS analysis. Extracts were analyzed for 14 pharmaceuticals in a single LC–MS/MS analysis with an electrospray ionization source operated in positive ion mode using MRM. Analytes were separated on a BEH Phenyl column (1.0 × 100 mm 1.7 μm) equipped with 0.2 μm inline filter. The LC–MS/MS methodology is described in detail in the supporting information section (Supplemental File 2; see also Batt and Aga, 2005).

Percent recovery for each analyte was calculated in a laboratory fortified distilled water blank and the matrix spike control sample, which were included with each extraction batch for a total of thirteen distilled water and matrix spike samples. Due to the complexity of the sample matrix, the acceptable target recoveries were set between 70% and 130% for compounds with an exact match isotopic standard and 50% and 150% for compounds without an exact match isotopic procedural internal standard. Reported data was not corrected using matrix spike recovery, instead the addition of isotopically labeled procedural internal standards was used to account for sample-to-sample matrix variations. Cimetidine, betamethasone, 2-hydroxyibuprofen, glipizide, and glyburide were excluded from data analysis since, in the vast majority of samples, these analytes failed method quality standards. Any analyte detected in either a field blank or laboratory blank were treated as estimated (flagged with a "B" flag) if the concentration of the analyte in the sample was less than ten times the blank concentration. The average of duplicate concentration measurements from an individual site was used in the reported data analysis.

2.4. Data analysis

Data analysis was performed using R 2.14.2 (R Development Core Team, 2012), using built-in functions and functions from the standard base packages. Effect level parameters of minimum daily dose (DdMin), maximum plasma concentration after a minimum dose (Cmax), fraction bound to plasma proteins (Fb), lowest minimum inhibitory concentration (MIC), and antibiotic breakpoint (BP), as well as the modes of action (MOAs), and predicted environmental concentration (PEC) listed in Supplemental File 1 were adapted from Kostich and Lazorchak (2008); or from Batt et al. (2008).

3. Results and discussion

3.1. Measured concentrations

A summary of occurrence data is presented in Table 1. Detailed plant-by-plant data for each analyte, including quality control flags is provided in Supplemental File 3. Of the 63 analytes measured, 43 were detected at least once. The 20 analytes we did not detect include 14 that were targeted because they appeared in our previous prioritization. That prioritization was driven by marketing data, and did not incorporate estimates of wastewater removal rates since that parameter is uncharacterized for the vast majority of pharmaceuticals. The absence of these analytes in effluent suggests that they are readily degraded within wastewater treatment facilities, diverted into the biosolids waste stream, or their usage rates are overestimated by the marketing data-based model. One API (hydrochlorothiazide, a diuretic used for the treatment of hypertension whose aquatic concentration has rarely been reported) was detected in all 50 effluents examined. In addition, metoprolol (an antihypertensive), atenolol (another antihypertensive), and carbamazepine (an anticonvulsant also used for other neurological and psychiatric conditions) were detected in more than 90% of effluents examined.

Our summaries of concentration data incorporated only data that was not flagged as estimated (see Supplemental File 3). The highest concentration measured for any API was 5300 ng/L (see Table 1) for valsartan (an antihypertensive), which also had the highest average concentration (1600 ng/L) across all 50 samples. The peak concentrations we saw for several analytes (i.e. ibuprofen) were somewhat lower than the highest concentrations reported in some other studies (reviewed in Kostich et al., 2010), but as we describe in the following sections, the conclusions from this study and from our previous summary of literature results (Kostich et al., 2010) are consistent with one another. In part, differences in concentrations reported here and those reported elsewhere in the literature may reflect differences in sampling locations or analytical methodologies. They may also reflect the contrast between our 24-h composites, versus the grab samples used in some other studies. In addition, we only sampled plants once, during the colder months of the year. This may prove advantageous for detecting analytes from pharmaceuticals with higher usage rates during winter months (i.e. antipyretics), and pharmaceuticals which are less efficiently removed during wastewater treatment in winter weather (see, for instance, Nelson et al., 2010). Conversely, it may lead to our study underestimating peak concentrations of pharmaceuticals that are used more in warmer weather (i.e. antihistamines). More detailed studies on the daily and seasonal profiles of effluent concentrations would be helpful for understanding the temporal dynamics of contaminant loading.