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Evaluation of concentrations of pharmaceuticals detected in sewage influents in Japan by using annual shipping and sales data

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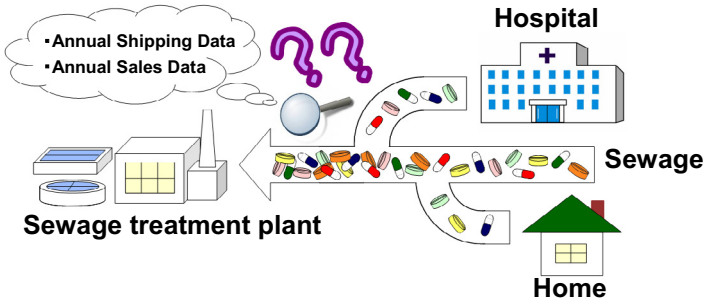
HIGHLIGHTS

- A year-round survey of pharmaceuticals in sewage influents was conducted.
- Two-type predictions were made on the basis of the shipping and sales data.
- Corresponding trend was seen in both based on shipping volumes or sales volumes.
- Better corresponding trend was found on the predictions made on the shipping volumes.

GRAPHICAL ABSTRACT



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ABSTRACT

A year-round monitoring survey of sewage flowing into sewage treatment plants located in urban Japan was conducted by targeting seven representative pharmaceutical components—atenolol (ATL), ciprofloxacin (CFX), clarithromycin (CTM), diclofenac (DCF), diltiazem (DTZ), disopyramide (DSP), and sulpiride (SPR)—detected in the river environment. For each of these components, two types of predicted concentration were estimated on the basis of two types of data (the shipping volume and sales volume of each component). The measured concentration of each component obtained through the survey and the two types of estimated predicted concentration of each component were then compared. The correspondence ratio between the predicted concentration estimated from the shipping volume of the component and the measured concentration (predicted concentration/measured concentration) was, for ATL, 3.1; CFX, 1.4; CTM, 1.4; DCF, 0.2; DTZ, 0.9; DSP, 11.6; and SPR, 1.1. The correspondence ratio between the predicted concentration estimated from the sales volume of the component and the measured concentration was, for ATL, 0.5; CFX, 1.1; CTM, 0.8; DCF, 0.1; DTZ, 0.2; DSP, 0.7; and SPR, 0.8. Although a generally corresponding trend was seen regardless of whether the prediction was based on shipping volume or sales volume, the predicted concentrations estimated from the shipping volumes of all components expect DSP were found, to our knowledge for the first time in Japan, to correspond better than those based on sales volumes to the measured concentrations. These findings should help to improve the prediction accuracy of concentrations of pharmaceutical components in river waters.

1. Introduction

In recent years, the problem of environmental pollution of rivers by pharmaceutical components has been reported all over the world. Many studies are being conducted, beginning with research aimed at understanding pollution status (Kolpin et al., 2002; López-Serna et al., 2010; Silva et al., 2011) followed by assessing

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adverse effects of pharmaceuticals remained due to the incomplete removal at sewage treatment plants (STPs) (Daughton and Ternes, 1999; Kolpin et al., 2002; Carlsson et al., 2006; Komori et al., 2013; Vasquez et al., 2014), and proposing recommendations for improving environmental risk assessment of human pharmaceuticals (Ågerstrand et al., 2015).

More than 90% of Japanese urban areas are covered by sewerage systems (Japan Sewage Works Association, 2013). The contribution of STPs as loading sources of pollutants in river environments is therefore large. The contribution of not only pharmaceutical components but also endocrine-disrupting chemicals such as estrogen as pollutant loads is reported by some to be as high as 50% to nearly 100% (Azuma et al., 2013; Kumar et al., 2014). Importance of STPs for lowering the levels of PPCPs in sewage is further noticed by showing the stability of cytostatic agents in sewage before entering into STPs after discharge from hospital (Ferrando-Climent et al., 2013). In addition, the Japanese pharmaceutical market is the second largest in the world after the United States (Ministry of Health Labour and Welfare, Japan, 2013).

Therefore, predicting the concentrations of pharmaceutical components in the influents of STPs is very important for improving the accuracy of prediction of the concentrations of pharmaceutical components in river environments (Johnson et al., 2008; Blair et al., 2013), conducting toxic impact assessments on riverine ecosystems (Huschek et al., 2004; Al Aukidy et al., 2012), and assessing the environmental risks of, for example, the increasingly researched problem of drug-resistant organisms emerging from aquatic environments (Kümmerer, 2009).

To be able to predict the concentrations of pharmaceutical components flowing into STPs, a primal request is information on the use of pharmaceuticals (FDA, 1998; EMEA, 2006). The available statistical information is represented by prescription-based data on the amounts of pharmaceutical components used (Huschek et al., 2004; EMEA, 2006) and market sales volume data (FDA, 1998; Tauxe-Wuersch et al., 2005). Some studies have already used these statistical data to examine ratios of excretion in unchanged form after pharmaceutical administration, amounts of water used per day per person, and rates of removal at STPs to estimate the predicted concentrations of pharmaceutical components in sewage and river water (Ferrari et al., 2003; Carballa et al., 2008; Besse et al., 2012; Oosterhuis et al., 2013). Correspondence ratios (predicted concentration/measured concentration) between predicted concentrations estimated by using the methods mentioned above and measured concentrations have been reported by these studies. Using concentrations predicted on the basis of the amounts used, correspondence ratios have been in the range of 1.4–38.4 for the antiinflammatory agent diclofenac, 0.2–22.1 for the psychotropic agent carbamazepine, 0.3–1.5 for the antimicrobial agent sulfamethoxazole, and 0.1–0.2 for the antihypertensive agent metoprolol (Ferrari et al., 2003; Carballa et al., 2008). Using concentrations predicted on the basis of sales volumes, the correspondence ratios have been in the ranges of 0.3–1.7 for diclofenac (Tauxe-Wuersch et al., 2005; Oosterhuis et al., 2013) and 2.0–3.3 for carbamazepine (Oosterhuis et al., 2013), and 38.8 for the anticancer agent cyclophosphamide (Besse et al., 2012). Although there are differences of about 10 times between the two types of predicted concentration and the measured concentration, the order of magnitudes have been mostly in agreement. Nevertheless, to our knowledge, no study has yet predicted concentrations on the basis of the volumes of pharmaceuticals shipped into the market; moreover, the correspondence between predicted and measured concentrations is mostly unknown.

In Japan, two types of statistics are available. One type is statistics on annual shipping volumes of pharmaceuticals available in the market (Ministry of Health Labour and Welfare, Japan, 2012), as surveyed by the government, and the other type is statistics on annual sales volumes of pharmaceuticals (Jiho, 2012b), as provided by private businesses as part of market research. In Japan, one report has already predicted the concentrations of pharmaceutical components in aquatic environments and has attempted to assess the correspondence between estimated and measured concentrations, targeting some of the components of anti-influenza and other agents (Azuma et al., 2012). However, further studies are still needed on the remaining components.

Given this situation, among the many pharmaceutical components available in Japan, this study focused on those for which statistical information on both shipping volume and sales volume, and excretion rates could be obtained and those that have frequently been detected in sewage and river waters. As representative pharmaceutical components meeting these criteria (Kolpin et al., 2002; López-Serna et al., 2010; Silva et al., 2011), the following seven components were chosen as the target and a year-round monitoring survey of the sewage influents flowing into three STPs located in urban Japan was conducted. The chosen components were the antimicrobial agents ciprofloxacin (CFX) and clarithromycin (CTM), the psychotropic agent sulpiride (SPR), the antinflammatory agent diclofenac (DCF), the antihypertensive agents atenolol (ATL) and diltiazem (DTZ), and antiarrhythmic agent disopyramide (DSP). The six components of these components except DCF are classified as the prescription pharmaceuticals in Japan which include newly released drugs having strong pharmacological effects, sometimes with high side-effects, therefore have a high potent risk for environmental pollution when erosion occurred into the environmental water. The last component, DCF, was selected as an additional target drug belonged to the over-the-counter drug, because this drug was widely used in Japan as a representative antiinflammatory drug and all information necessary to predict its concentration were available. By using information on the shipping volumes (Ministry of Health Labour and Welfare, Japan, 2012) and sales volumes (Jiho, 2012b) of these pharmaceutical components, the concentration of each of these components in the influents of STPs were separately predicted. Correspondences were then evaluated between the measured concentration obtained through the survey and the two types of predicted concentration.

2. Materials and methods

2.1. Chemicals and reagents

ATL (purity 98%) was purchased from Wako Pure Chemical Industry, Ltd. (Osaka, Japan). CFX (purity 99%) were purchased from MP Biomedicals, LLC (Tokyo, Japan). CTM (purity 99%), DCF (purity 98%), DTZ (purity 98%), DSP (purity 99%), and SPR (purity 98%) were purchased from Wako Pure Chemical Industry, Ltd. (Osaka, Japan). The annual shipping data, sales data, and ratios of excretion as unchanged drugs after ingestion are given in Table S1. LC-MS-grade solvents (methanol, acetone), formic acid, and ascorbic acid were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Individual standard stock solutions of ATL, CFX, CTM, DCF, DTZ, DSP, and SPR at 1 mg/100 mL were prepared in methanol and stored at −30 °C.

2.2. Sampling

Sewage influents were collected at three STPs (A, B, and C) located in the Yodo River system, which is one of the biggest basins in Japan and is home to 12 million people (Lake Biwa-Yodo River Water Quality Preservation Organization, Japan, 2012). The separate sewage system was operated in the whole basin. The properties of the STPs and numbers of hospitals surveyed are shown in Table S2. One-liter samples as 24-h composite samples in