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Research paper

Prioritization methodology for the monitoring of active pharmaceutical ingredients in hospital effluents

Silwan Daouk [a, *], Nathalie Chèvre [b], Nathalie Vernaz [a], Pascal Bonnabry [a, c], Pierre Dayer [d], Youssef Daali [d], Sandrine Fleury-Souverain [a]

[a] Geneva University Hospitals (HUG), Pharmacy, Geneva, Switzerland
[b] University of Lausanne (UNIL), Institute of Earth Surface Dynamics, Lausanne, Switzerland
[c] University of Geneva, University of Lausanne, School of Pharmaceutical Sciences, Geneva, Switzerland
[d] Geneva University Hospitals (HUG), Clinical Pharmacology and Toxicology, Geneva, Switzerland

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ABSTRACT

The important number of active pharmaceutical ingredients (API) available on the market along with their potential adverse effects in the aquatic ecosystems, lead to the development of prioritization methods, which allow choosing priority molecules to monitor based on a set of selected criteria. Due to the large volumes of API used in hospitals, an increasing attention has been recently paid to their effluents as a source of environmental pollution. Based on the consumption data of a Swiss university hospital, about hundred of API has been prioritized following an OPBT approach (Occurrence, Persistence, Bioaccumulation and Toxicity). In addition, an Environmental Risk Assessment (ERA) allowed prioritizing API based on predicted concentrations and environmental toxicity data found in the literature for 71 compounds. Both prioritization approaches were compared. OPBT prioritization results highlight the high concern of some non steroidal anti-inflammatory drugs and antiviral drugs, whereas antibiotics are revealed by ERA as potentially problematic to the aquatic ecosystems. Nevertheless, according to the predicted risk quotient, only the hospital fraction of ciprofloxacin represents a risk to the aquatic organisms. Some compounds were highlighted as high-priority with both methods: ibuprofen, trimethoprim, sulfamethoxazole, ritonavir, gabapentin, amoxicillin, ciprofloxacin, raltegravir, propofol, etc. Analyzing consumption data and building prioritization lists helped choosing about 15 API to be monitored in hospital wastewaters. The API ranking approach adopted in this study can be easily transposed to any other hospitals, which have the will to look at the contamination of their effluents.

1. Introduction

Active pharmaceutical ingredients (API) are continuously released into the aquatic environment and are thus considered as 'pseudo-persistent' pollutants (Daughton, 2003; Kümmerer, 2009a). Their inputs are diverse and may come from human and animal use, waste disposal and/or manufacturing (Daughton, 2003; Kümmerer, 2010). Generally, urban wastewater treatment plants (WWTP) are the main contributors of API residues inputs into the aquatic ecosystems (Götz et al., 2010b; Kümmerer, 2010; Michael et al., 2013). A small proportion of this point source pollution comes however from hospitals and health care facilities, which differentiate itself from domestics ones by the nature of administrated molecules (Kümmerer, 2001; Mullot, 2009). Globally, hospitals represent indeed only a small proportion of the urban API load source found at the watershed outlet: <10% (Kümmerer, 2010), <15% (Ort et al., 2010; Le Corre et al., 2012), 20–25% (Helwig et al., 2013). But, this fraction can vary from 3 to 74% according to the compound type and the hospital beds/inhabitants ratio of the watershed (Santos et al., 2013).

Once in the environment, API residues can cause some adverse effects in wildlife, such as fish feminization by synthetic hormones (Fent et al., 2006; Santos et al., 2010), or fish and birds kidney impairment by the non-steroidal anti-inflammatory drug diclofenac (Oaks et al., 2004; Hoeger et al., 2005). The environmental toxicity of API is generally appreciated by ecotoxicological tests, which give dose–response curves, from which water quality

* Corresponding author. Laboratoire Contrôle Qualité, Pharmacie des Hôpitaux Universitaires de Genève, 4 Rue Gabrielle Perret-Gentil, 1211 Genève 14, Switzerland.
E-mail address: Silwan.Daouk@hcuge.ch (S. Daouk).

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criteria are derived, such as predicted no effect concentrations (PNEC) (European Commision, 2003). Unfortunately, experimental values are scarce (Chèvre, 2014). They cannot be replaced by theoretical ones, such as the ones modeled by quantitative structure–activity relationships (QSAR) approaches (Escher et al., 2011; Jean et al., 2012; Orias and Perrodin, 2013). Therefore, PNEC values found in the literature are scarce, often modeled, and can vary as much as three orders of magnitude between studies according to conditions and endpoints (Helwig et al., 2013).

Prioritization methods applied to pharmaceuticals are generally based on consumption data and a simplified risk assessment for the environment and/or human health (EMEA, 2006; de Jongh et al., 2012; Le Corre et al., 2012). Nevertheless, other parameters are most of the time also considered such as environmental persistence, bioaccumulation factor, and mode of action and/or analytical feasibility (Besse and Garric, 2008; Perazzolo et al., 2010; Jean et al., 2012; Ortiz de Garcia et al., 2013). Thus, the elaboration of a priority list of pharmaceuticals strongly depends on the pertinence of the chosen criteria, and also on the exhaustiveness and the quality of the available data (Mullot, 2009; Coutu et al., 2012). Among the numerous approaches applied for prioritizing substances, the persistence, bioaccumulation and toxicity (PBT) approach is used in Europe in the framework of the registration, evaluation, authorization and restriction of chemicals (REACH), as well as in specific studies dealing with pharmaceuticals (Wennmalm and Gunnarsson, 2009; Ortiz de Garcia et al., 2013). It consists of giving a ranking of concern according to their PBT properties, but these latter are not available for many compounds leading researchers to use QSAR models to predict them (Pavan and Worth, 2008).

Another method for prioritizing chemicals, such as pharmaceuticals, is proposed by the European Medicines Agency. It consists in a tier-based environmental risk assessment procedure for API which comprises two phases (EMEA, 2006): the estimation of exposure (phase I) and the environmental fate and effects analysis (phase II). Phase I comprises a PBT approach and the calculation of the predicted environmental concentrations (PEC): if the API shows a bioaccumulation tendency (Log K_{ow} > 4.5) or a PEC > 0.01 μg/L, then a phase II is needed. Phase II deals with the calculation of the environmental risk quotient (RQ) as the ratio between exposure (PEC) and effects (PNEC). This procedure has been adopted by several authors and adapted according to the study's specific needs (Besse and Garric, 2008; Mullot, 2009; Perazzolo et al., 2010; Coutu et al., 2013).

The objectives of the present study are manifold. First, it aims at elaborating a prioritization list of API based on consumption data of a university hospital and on their environmental persistence, bioaccumulation potential and ecotoxicity data found in the scientific literature. A weighting of the PBT properties is done according to the quality of data. Second, predictions of API concentrations in the hospital effluents and in surface waters, as well as of their environmental risk quotients are calculated, under the assumptions of on-site total consumption and mass conservation into the sewers. The results of both methods are compared and discussed. In the end, these prioritization and predictions should help choosing priority compounds to be measured in the hospital effluents and taking decisions for the hospital managers in order to reduce the inputs of pharmaceutical residues into the urban network and, subsequently, their potential adverse effects for the aquatic ecosystems.

2. Material and methods

2.1. Setting and consumption data collection

The Geneva University Hospitals (HUG) is one of the most important hospitals of Switzerland. It comprises eight hospitals and about 40 other health care facilities, providing both primary and tertiary care. In 2012, 8443.2 full-time equivalent collaborators and a total of 671′709 days of hospitalization were registered, for 1908 beds, 48′112 inpatients and over 860′000 outpatient consultations. The average daily water consumption was 762 m^3.

Aggregated data of drugs dispensed in both the inpatient and outpatient settings in 2012 were first obtained from the hospital pharmacy database using "Business Object®" software. These data correspond to the drugs ordered by the different medical units to the pharmacy to treat their patients, as well as returns (stock and delivery errors, leaving or deceased patients, etc.). The data gives an approximation of the yearly inpatient consumption of API by transforming the overall unit doses (UD) in grams of active ingredient while considering their dosages (Jean et al., 2012). It is worth to stress that only drugs purchased as a total package was taken into account. Also, the stock of each medical unit was considered but the stock difference between years was neglected. All confidential health information was removed to create anonymous analytic datasets in conformity with Swiss data protection regulations.

2.2. PBT prioritization

The prioritization procedure applied to active pharmaceutical ingredients (API) consumed in the Geneva university hospitals as a whole was adapted from previous studies (Besse and Garric, 2008; Perazzolo et al., 2010; Jean et al., 2012). Among the about 1000 API delivered by the hospital pharmacy in 2012, only about 150 API with more than 10′000 unit doses (UD) were first retained. Then, after conversion from UD to grams of API, only 84 API sold at more than 1 kg in 2012 were kept. To these, antineoplastic and immunomodulant drugs (Code L according to the Anatomical Therapeutic Classification; ATC) with more than 10′000 UD were added due to their inherent toxicity, giving a total of a hundred of API for the prioritization. Each API has been attributed 4 ranks, from 1 to 5, based on 4 criteria (Table 1): Occurrence (O), Persistence (P), Bioaccumulation (B) and Environmental Toxicity (T).

The occurrence (O) criteria was based on the excreted amounts in the hospital effluents, which was obtained by multiplying the consumed mass (M) by the excretion factor (F_{excr}), assuming that 100% of the amounts delivered by the pharmacy were used. Excretions factors (F_{excr}) in urine and feces as unchanged drugs were found in databases (www.uptodate.com; www.compendium.ch). When different values were reported, a mean value was calculated. The thresholds of 0.05, 0.5, 5 and 20 kg were chosen for the scoring according to the distribution of the excreted mass values and observed natural thresholds. Pro-drugs consumption was added to the one of its related drug: capecitabine − 5-fluorouracil; valaciclovir − aciclovir, etc. Indeed, when metabolized, pro-drugs end mainly as their related compound in the hospital sewers.

For the persistence (P) criteria, values of WWTP removal efficiency were found in the scientific literature for only 32 API with a

Table 1
Criteria thresholds for the ranking of API.

Rank	Occurrence	Toxicity	Bioaccumulation	Persistence
criteria	$Mass_{excr}$	PNEC[a] [μg/L]	Log K_{ow}	WWTP removal [%]
1	≤0.05 kg	>100	<1	≥80
2	≤0.5 kg	≤100	≥1	≥60
3	≤5 kg	≤10	≥2	≥40
4	≤20 kg	≤1	≥3	≥20
5	>20 kg	≤0.1	≥4.5	<20

[a] PNEC = Predicted no-effect concentration.

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