MODELLING DICLOFENAC AND IBUPROFEN RESIDUES IN MAJOR ESTONIAN SEASIDE CITIES

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Abstract. A theoretical model was developed to model the fate of two common pharmaceutical residues: diclofenac and ibuprofen in eight Estonian seaside cities that discharge their wastewaters directly into the Baltic Sea. The consumption rates of the active ingredients of diclofenac and ibuprofen from 2006-2014 were analysed. A decrease of 19.9% for diclofenac consumption and an increase of 14.1% for ibuprofen were found. The fate of diclofenac and ibuprofen were modelled by considering the human metabolism removal rate for pharmaceuticals, the removal rate of diclofenac and ibuprofen in activated sludge wastewater treatment plants (WWTP) and annual flow rates. An average decrease from 1 to 0.8 µg/l (decrease of 20%) for diclofenac and an increase from 11.4 to 13.4 µg/l (increase of 14.9%) for ibuprofen for the concentration in the effluents of the WWTP were modelled. The model gives us a good overview about the theoretical concentrations of pharmaceutical residues in the environment and is helpful for evaluating environmental impacts.

Keywords: diclofenac residues, fate of pharmaceuticals, ibuprofen residue, modelling pharmaceuticals, pharmaceutical residues in the environment.

Introduction

Pharmaceuticals used in human and veterinary medicine have become an important public health issue in recent years and are an emerging environmental problem, since they pose a threat to both the environment and humans. With an increasingly aging population over the world in recent years, a new problem has emerged: pharmaceutical residues in the environment (Zhou et al., 2009). Pharmaceutical residues have already been found in measurable concentrations (µg/l and ng/l) in lakes, seas, groundwater (diclofenac and ibuprofen in range of 0.03-0.06 µg/l and 0.004-0.04 µg/l accordingly) and drinking water and they have become an emerging environmental problem (Cleuvres, 2004; Fent et al., 2006; Li, 2014). There is no acute toxic effect of pharmaceuticals for humans, but the concerning issue is their chronic toxicity and bioaccumulation. Pharmaceuticals are constructed to be persistent, biologically active and to target specific metabolic pathways (Ternes, 1998; Heberer, 2002; Moreno-González et al., 2016).

In the 1990s in Pakistan, the incomprehensible dying of white-backed vultures (Gyps africanus), resulting in a 95% decrease in the population of vultures, was observed. In examining the reasons for the deaths, scientists investigated the primary food source of vultures, dead domestic livestock. A connection between the food source of vultures and the deaths was found, as diclofenac residue concentrations of 0.051-0.063 µg/g were detected when scientists analysed the kidneys of vultures (Oaks et al., 2004).

In other research, Dietrich and Prietz (1999) analysed the lethality and teratogenicity of diclofenac to zebrafish embryos. A lethal concentration of 489 ± 50 µg/l (LC50/96h) and an effect concentration of 90 ± 20 µg/l (EC50/96 h) was found (Dietrich et al., 1999; Schwaiger et al., 2004). An acute toxicity of ibuprofen for algae EC50/96 h 7100 µg/l was reported by Halling-Sørensen and Carina Carlsson and reported for Lepomis macrochirus (bluegill) a LC50 of 173 mg/l (Carlsson et al., 2006; Halling-Sørensen et al., 1998).

To date, there have been rather few studies that reported about pharmaceutical residues in the water environment in Estonia; hence, it is important to know the impact rate of pharmaceuticals in the Baltic Sea catchment area. The Baltic Sea is virtually a closed system, much like a lake, and very sensitive to the accumulation of different harmful substances. An important issue is that the Baltic Sea is an important source of food for Nordic countries, and the bioaccumulation of diclofenac and ibuprofen is known. Therefore, it is important to analyse the fate of different pharmaceuticals in the environment (Carlsson et al., 2006; Borecka et al., 2015; Moreno-González et al., 2016).

Stockholm University has found diclofenac and ibuprofen in different WWTP runoff areas in concentrations ranging from 0.2 to 7.1 µg/l and 0.1 to 0.2 µg/l and a total non-steroidal anti-inflammatory drugs (NSAID) concentration of 24 µg/l. In the same study, a bioaccumulation effect of NSAID on the blue mussel in the Baltic Sea was found (Ericson et al., 2010). Depending on various troubling studies, a new regional HELCOM status report is scheduled in February 2016, which will provide an extensive background to determine the possible harmful effects of pharmaceutical residues in the Baltic Sea. In Estonia, hazardous substances, including the content of priority substances in wastewater and stormwater effluents, should not exceed the environmental quality limit values of surface water.
bodies, as established by the Water Act. However, there are no limits determined for pharmaceuticals. There are already many promising treatment technologies for pharmaceutical residues removal, such as membrane bioreactor (MBR), activated carbon, advanced oxidation, UV irradiation and TiO\textsubscript{2} photocatalysis (Köhler et al., 2012; Giannakis et al., 2015; He et al., 2016). The easiest way is activated sludge process optimisation. For ibuprofen, a higher hydraulic retention time and sludge age means it has a good biological degradation rate (Miège et al., 2009).

In this study, we concentrated on two widely used pharmaceuticals NSAID: diclofenac and ibuprofen. These two pharmaceuticals have been chosen because there is no need for a prescription to buy these drugs; they are therefore used in large amounts, and their negative effect on the environment is well known.

Several previously published different models have estimated the concentrations of pharmaceutical residues in the effluents of WWTP. There are two ways to look at a model: (Khan, Ongerth, 2004; Zhang et al., 2015)

a) as a closed system, such as a hospital;

b) as a fate model from the consumer to the environment.

In a mathematical model from the consumer to the environment, two important parameters should be taken into account: the metabolism removal rate in human body and the removal rates of WWTP. In WWTP, we examine two main processes resulting in a decrease in concentrations of diclofenac and ibuprofen: these are the absorption of suspended solids and biodegradation (Kümmerer et al., 1997; Fent et al., 2006). Ibuprofen is biodegradable and normally more than 70% is removed in a WWTP (Fent et al., 2006). That means that there are lower pharmaceutical residues concentrations in effluent, but higher concentrations in sludge, which is often used in agriculture (Lillenberg, 2011).

The aim of this study was to model the fate of ibuprofen and diclofenac in major Estonian seaside cities to assess the need for a treatment step at WWTP to reduce the pharmaceutical residues in the effluent of WWTP that are discharging wastewater directly into the Baltic Sea. A second aim was to analyse the trend of pharmaceutical residues in Estonia.

**Material and Methods**

**Description of the model**

A theoretical model was compiled to evaluate the concentrations of diclofenac and ibuprofen in the effluents of the Tallinn, Narva, Kohtla-Järve, Kunda, Haapsalu, Pärnu, Kärdla and Kuressaare WWTP located close to the Baltic Sea, in the time period between 2006 and 2014. There are approximately 577,000 inhabitants in these chosen settlements, comprising 44% of whole Estonian population. The largest settlement is Tallinn with over 410,000 people. The model considers population, yearly consumption of diclofenac and ibuprofen, metabolism removal rates of drugs in the human body and WWTP removal rates.

![Location of WWTP where diclofenac and ibuprofen loads and concentrations in WWTP effluents were modelled](image)

**Data collection**

The population data for the time period between 2006 and 2014 for the eight cities of Tallinn, Narva, Kohtla-Järve, Kunda, Haapsalu, Pärnu, Kärdla and Kuressaare were obtained from Statistics Estonia. Data about the consumption of diclofenac and ibuprofen were requested from the Estonian Agency of Medicine. Data about WWTP discharges were requested from National Water Use Database of the Estonian Environment Register.
**Data analysis**

The total amount of active substance for diclofenac and ibuprofen was calculated. As diclofenac is often sold as gel with an active substance concentration of 5%, there are also pharmaceuticals with ibuprofen content for injection.

**Consumption of diclofenac and ibuprofen**

As there are no separate data for the consumption of pharmaceuticals in Estonian settlements, a simplification was made. At first, the yearly consumption from 2006 to 2014 of the active substance of diclofenac and ibuprofen was calculated in \( K_{\text{yearly-u}} \) per person, using the entire Estonian consumption:

\[
K_{\text{yearly-u}} = \frac{\text{Consumption of pharmaceutical}}{\text{Population}}
\]

In order to calculate the consumption of diclofenac and ibuprofen for the study area cities, the population of these cities was multiplied with the consumption rate \( K_{\text{yearly-u}} \).

**Load calculation**

A theoretical model in MS Excel was prepared to calculate the yearly loads and average concentration of diclofenac and ibuprofen in the Baltic Sea. In the model, two constants were used: the metabolism removal rate in the human body for diclofenac and ibuprofen \( M_{\text{removal}} \) and the removal rate in an activated sludge WWTP \( \text{WWTP}_{\text{removal}} \). The metabolism removal rate was studied and reported by Lienert (Lienert et al., 2007) and the removal rates in WWTP by Miège (Miège et al., 2009). In Miège’s study, data on diclofenac removal from 37 WWTP and data on ibuprofen removal from 51 WWTP is reported (Miège et al., 2009). The average from these 37 WWTP was used to calculate the removal constant.

<table>
<thead>
<tr>
<th></th>
<th>Metabolism removal rate</th>
<th>WWTP removal rate</th>
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<tbody>
<tr>
<td><strong>Diclofenac</strong></td>
<td>0.84 (0.78-0.94)</td>
<td>0.32 (0.19)</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>0.70 (0.71-0.51)</td>
<td>0.74 (0.29)</td>
</tr>
</tbody>
</table>

1 (Lienert et al., 2007; ter Laak et al., 2010), minimum and maximum values are in the brackets.

2 (Miège et al., 2009; ter Laak et al., 2010), standard deviation in the brackets.

3 (Lienert et al., 2007; ter Laak et al., 2010), minimum and maximum values are in the brackets.

4 (Miège et al., 2009; ter Laak et al., 2010), standard deviation in the brackets.

By using the model, the yearly load of diclofenac and ibuprofen from eight Estonian cities on the Baltic Sea was calculated as followed:

\[
K_{\text{yearly-load}} = K_{\text{population}} \times K_{\text{yearly-u}} \times (1 - M_{\text{removal}}) \times (1 - \text{WWTP}_{\text{removal}})
\]

**Results and Discussion**

Figure 2 shows the consumption of diclofenac and ibuprofen in Estonia from 2006 to 2014.
A remarkable decrease in diclofenac consumption of 19.9% was found, though it was just the opposite in the case of ibuprofen, as a consumption increase of 14.1% was discovered. The increase of the usage of some pharmaceuticals can be connected with population aging (Arnold et al., 2014). The decreasing usage of diclofenac can be connected with changes in the law during this period; some common diclofenac pharmaceuticals have required a prescription since 2007. A second reason can be the announcement from the European Medicines Agency that diclofenac is not a safer analgesic than ibuprofen, because it can cause cardiovascular diseases like heart attack and stroke. In Germany, a remarkable increase of 116% in the consumption of ibuprofen was recorded from 2002 to 2009, though it was only 4% for diclofenac (Bergmann, et al., 2011).

In Figure 3, the modelled discharge loads of diclofenac for Tallinn, Narva, Kohtla-Järve, Kunda, Haapsalu, Pärnu, Kärdla and Kuressaare are outlined. The main loads of diclofenac residues originating from three largest cities of Tallinn, Narva and Pärnu amount to a total average yearly amount of 30 kg. In Pärnu, a decrease in the total load of diclofenac over 23.1% is observed. Narva has seen a decrease of 26% and Haapsalu of 24.7%.

In Figure 4, the discharge rates of ibuprofen residues to the Baltic Sea are shown. Ibuprofen discharge rates increased by more than 15% from 2006 to 2014. From 2006 to 2010, a decrease of consumption in all cities was found, which was due to the usage of ibuprofen.
In Narva, Pärnu, Haapsalu, Kohtla-Järve, Kärdla and Kunda, an average increase of 7.5% for ibuprofen discharge loads was found. In Tallinn, the consumption rates have increased from 293 kg to 361 kg in connection with the growing consumption rates in Estonia and with the increasing population trend in Tallinn.

Figure 5 shows the modelled average annual concentrations of diclofenac residues in the effluents of WWTP covered by our research. The highest average concentrations were found in Kunda and Kärdla, with values of 1.4 and 1.5 µg/l, accordingly. It can be explained by smaller flow rates per capita, which in turn results from a separated sewer system in use. In Estonia’s largest city, Tallinn, the decrease in diclofenac concentration of 17.8% was modelled. The average concentration in our research-enclosed cities has decreased from 1 to 0.8 µg/l (decrease of 20%). The German Ministry for the Environment analysed 198 WWTP effluents in Germany and found diclofenac in concentrations from 0.4 to 10 µg/l (Rohweder, 2003). In his article based on scientific journals around the world, Miège found a diclofenac concentration in the effluents of 46 WWTP from 0.035 to 1.72 µg/l (Miège et al., 2009). By comparing our modelled data with prior studies, we see rather good compatibility (Figure 5).

Altmets found in her environmental risk assessment that a diclofenac predicted environmental concentration of 0.59 µg/l has a high environmental risk because it is persistent and bioaccumulative (Altmets, 2012). Our modelled data showed higher values in most of the WWTP outlets.

**Fig. 5.** Modelled average diclofenac concentrations in eight Estonian seaside WWTP effluents, from 2006 to 2014

In Figure 6, the modelling results of average ibuprofen residue concentrations in eight WWTP effluents of Tallinn, Narva, Kohtla-Järve, Kunda, Haapsalu, Pärnu, Kärdla and Kuressaare are shown.

**Fig. 6.** Modelled average ibuprofen concentrations in eight Estonian seaside WWTP effluents from 2006 to 2014
Similar to diclofenac, the highest average concentrations are in Kunda and Kärdla, with 18.3 and 18.8 µg/l in connection with smaller flow rates in the recent years. The average concentration of ibuprofen has increased in the eight described cities from 11.4 to 13.4 µg/l. Together, in all eight cities, an average concentration increase for ibuprofen residues of 14.9% was seen. The previously described German report found ibuprofen in concentrations from 0 to 3.7 µg/l in the effluents of 178 WWTP (Rohwedder, 2003). Miège in his study found ibuprofen in the range of 0.04 to 1.7 µg/l (Miège et al., 2009). In comparison to the modelling results obtained with the prior studies, we observed that the theoretical model for ibuprofen is overrating the concentrations by more than 64%. The exaggeration can be due to a variety of possible reasons such as the greater proportion of stormwater or higher accumulation into wasted activated sludge, which is removed separately.

In Altmets’s environmental risk assessment for ibuprofen, the environmental risk was deemed to be insignificant (Altmets, 2012). Despite this, it is necessary to identify real values for ibuprofen, since our model showed rather high concentrations.

**Conclusion**

In Estonia, the consumption of diclofenac has decreased from 804 to 644 kg and for ibuprofen it has grown from 12749 to 14836 kg in time period between 2006 and 2014. Diclofenac usage was rather decreasing, but an increasing trend was observed for ibuprofen, which is due to many reasons such as aging population and longer life expectancy. To evaluate the risks for the environment, the concentration of the pharmaceuticals in the wastewater are more relevant than the consumption. For diclofenac in eight different cities on the studied period, an average concentration of 0.8 µg/l and for ibuprofen 10.5 µg/l was modelled.

The environmental risk of diclofenac, based on different studies has been categorised as high. Using this modelled data, we are able to forecast the trends of consumption rates and concentrations of pharmaceutical residues in WWTP effluents. The model is not totally comparable with the real concentrations of diclofenac and ibuprofen, but it gives us a good overall picture and trend, as well the knowledge that we need to continue with this field of study.

A future study in Estonia is required to monitor in more detail the real concentrations of pharmaceutical residues in the effluents of WWTP and in the environment, with the aim of making a decision on an additional treatment step and treatment technology in WWTP for the removal of pharmaceuticals where it is deemed appropriate.

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