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RESEARCH ARTICLE

Do concentrations of pharmaceuticals in sewage reflect prescription figures?

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Abstract In recent years, it has been demonstrated that sewage-based epidemiology can deliver interesting information on trends in illicit drug consumption. However, until now, no real evidence exists that the measured concentrations of drugs in sewage can be exactly correlated with the amounts of drugs used by a specific population. This study aimed therefore at correlating detailed monthly prescription figures of 11 pharmaceuticals (atenolol, bisoprolol, citalopram, fluoxetine, venlafaxine, losartan, telmisartan, valsartan, carbamazepine, metformin, and tramadol) with measured concentrations of these compounds in influent sewage from five sewage treatment plants in Belgium. For 7 out of the 11 substances, a ratio between loads calculated from the prescription figures and loads calculated from measured concentrations in the range of 0.30–3.00 was observed. For four pharmaceuticals (atenolol, bisoprolol, telmisartan, and venlafaxine), the observed relationship was less pronounced. The manuscript gives an overview of the possible uncertainties that are related with the calculated correlations. This study highlights the need for gathering all the necessary information regarding sewage sampling, stability of substances in sewage, pharmacokinetics, and analytical method performance when sewage-based epidemiology studies are performed.

Keywords Pharmaceuticals · Sewage · Wastewater · Predicted loads · Measured loads · Sewage-based epidemiology

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Introduction

The presence of pharmaceuticals in the aquatic cycle has received increasing attention in the last decade (Fatta-Kassinos et al. 2011; Verlicchi et al. 2012). A wide range of pharmaceuticals and their metabolites are continuously introduced into the aquatic environment through human consumption, excretion, and insufficient removal during sewage treatment. This leads to a constant exposure of the aquatic environment to a large cocktail of bioactive molecules which eventually can affect water quality and can have an impact on the ecosystem, drinking water supplies, and human health (Brausch et al. 2012; Huerta et al. 2012). The measurement of pharmaceuticals in different aquatic compartments (influent and effluent

sewage, surface water, ground water, and drinking water) at often low concentrations (ng/L to μg/L) became possible with the development of sensitive hyphenated analytical techniques such as liquid chromatography coupled to mass spectrometry (Petrovic et al. 2010; Richardson 2010; Hernandez et al. 2015). Roughly estimated, around 3000 biologically active chemical compounds have been detected in the aquatic environment and quantified with the available analytical techniques (Richardson and Ternes 2011).

Recently, the presence of biologically active compounds in sewage has been applied for a different purpose. Measured concentrations of illicit drugs and their metabolites (e.g., cocaine, ecstasy, amphetamine, methamphetamine, and cannabis) in untreated (influent) sewage have been used to back-calculate the amount of these substances consumed by a specific population (i.e., the population that lives in a catchment area of a sewage treatment plant (STP)) (Castiglioni et al. 2014; van Nuijs et al. 2011). This approach, called sewage-based epidemiology (SBE), can deliver important information on temporal and geographical trends in the consumption of illicit drugs, and several studies have been performed on the local, national, and international level (Castiglioni et al. 2014). SBE assumes that the measured concentrations of illicit drugs and their metabolites in influent sewage can be directly correlated with the amount of these substances that are used by the population under investigation. However, more evidence-based scientific data is necessary to support this assumption (Castiglioni et al. 2014). Within this context, the possibility of correlating concentrations of pharmaceuticals measured in influent sewage with detailed prescription figures becomes highly relevant.

Until now, only a few studies have been carried out that attempted to correlate measured influent sewage concentrations of pharmaceuticals with indicators of the actual use of these substances (national consumption estimates, selling figures, etc.). Tauxe-Wuersch et al. compared the measured concentrations of five pharmaceuticals (four non-steroidal anti-inflammatory drugs (NSAIDs) and clofibric acid) in influent sewage from three STPs in Switzerland with annual, national consumption data (Tauxe-Wuersch et al. 2005). They observed a relationship between predicted and measured concentrations within one order of magnitude, but measured concentrations were for all compounds higher than the predicted concentrations. Carballa et al. compared the annual Spanish consumption data of 17 pharmaceuticals with measured concentrations in sewage from two STPs in Galicia and Catalonia (Carballa et al. 2008). For some compounds, a good correlation was observed, while for others, no clear relationship was seen. Morasch et al. came to similar conclusions by comparing measured concentrations of 31 pharmaceuticals in influent sewage from 1 STP in Switzerland with annual, national consumption data (Morasch et al. 2010). Lai et al. compared measured concentrations of 5 pharmaceuticals in 12 influent sewage samples from 1 STP in Australia with annual, national consumption data (Lai et al. 2011). In general, good correlations were observed, except for venlafaxine. Finally, Verlicchi et al. performed a comparison for 11 antibiotics and carbamazepine concentrations in influent sewage from 1 Italian STP with annual, national consumption data (Verlicchi et al. 2014). Also, here, a variable correlation was observed.

These abovementioned studies have several disadvantages which possibly affect the observed correlations: (1) concentrations measured in daily samples are correlated with annual consumption data, (2) concentrations measured in specific geographical locations (i.e., catchment area of STP) are correlated with national consumption data, and (3) some of the selected compounds (antibiotics, benzodiazepines, and NSAIDs) are prone to a strong variability in consumption and dosage over the course of time.

To bridge some of these gaps, the present study aimed at performing a more reliable correlation between measured influent sewage concentrations of pharmaceuticals and actual consumption of these substances by addressing a particular study setup: 11 pharmaceuticals were selected that can be acquired only after medical prescription and assumed to be used once daily at a stable dose and obtained detailed prescription figures (amount of defined daily doses (DDDs) per postal code and per month) and influent sewage samples for five selected STP catchment areas.

Materials and methods

Pharmaceuticals and prescription figures

The selection of pharmaceuticals suitable for the purpose of this study was made based on the following criteria:

1. A relatively stable consumption frequency and dosing regime and exclusively available through medical prescription. For example, blood pressure-lowering drugs such as angiotensin II receptor antagonists and beta blockers are normally administered once daily at a stable dose.
2. The pharmaceuticals under investigation have to be used widely throughout the general population in significant doses in order to be detectable and quantifiable in influent sewage samples.
3. The substances under investigation need to have a known (urinary) excretion pattern in order to be able to perform back-calculations.

Based on these criteria, the following compounds were selected: atenolol, bisoprolol, citalopram, fluoxetine, venlafaxine, losartan, telmisartan, valsartan, carbamazepine, metformin, and tramadol. For losartan, besides the parent

compound also its major metabolite, losartan carboxylic acid, was measured in sewage as indicator for losartan consumption. Table 1 gives additional information on the studied pharmaceuticals.

Detailed prescription figures were obtained from the National Institute for Health and Disability Insurance (RIZIV), which collects the data of prescribed pharmaceuticals in Belgium for reimbursement purposes up to the individual level. For this study, the amount of prescribed DDDs per postal code (based on the residence address of the patient) and per month in 2007 was obtained for each of the Anatomical Therapeutic Chemical (ATC) codes that contained one of the 11 selected pharmaceuticals. The variability in the consumption of the pharmaceuticals under investigation was assessed by calculating the relative standard deviation (RSD) of the monthly amount of prescribed DDDs over a one-year period. The mean amount of DDD per month was further transformed into a daily amount of DDDs to make the correlation (see "Calculations").

Sampling sites and sample collection

Influent sewage samples were collected from five STPs in Belgium in 2007: STP 1 (population equivalents, 59,400), STP 2 (population equivalents, 63,000), STP 3 (population equivalents, 58,500), STP 4 (population equivalents, 43,200), and STP 5 (population equivalents, 54,900). In each STP, one 24-h composite influent sewage sample was collected in a time-proportional manner with 10 min sampling intervals, and the flow rate of the total influent sewage stream corresponding with each sample was recorded. After collection, samples were immediately brought at −20 °C and transported to the laboratory for further analysis.

Analytical methodology

Sewage samples were analyzed for the selected pharmaceuticals with two validated analytical methods, which were described in detail earlier (Tarcomnicu et al. 2011; van Nuijs et al. 2010). Briefly, after addition of suitable labelled internal standards, a solid-phase extraction on Oasis MCX or Oasis HLB was performed on 50 mL of filtered influent sewage and the resulting extracts were analyzed by liquid chromatography–tandem mass spectrometry (LC-MS/MS) using specific multiple reaction monitoring (MRM) transitions. The quality of the analyses was assured by in-batch analysis of in-house prepared quality control samples. More details on the performance of the analytical methods can be found in the supporting information (Table SI1 and Table SI2). Measured concentrations are shown in Table SI3.

Calculations

Because the STP catchment areas under investigation did not correspond with the boundaries of a single city, we had first to investigate which postal codes are linked with the STP catchment areas. This was performed via the MapInfo software (Pitney Bowes, Stamford, USA) through overlaying maps of the STP catchment areas and the Belgian territory. The total amount of daily DDDs per catchment area was then obtained by summing the DDD values of the relevant postal codes. By multiplying the total DDD value per STP with the value of the

Table 1 Information on the investigated pharmaceuticals. The correction factor is derived from the percentage of an administered dose that is recovered in the urine

Pharmaceutical	Class	ATC codes (available in Belgium)+DDD value[a]	Correction factor[b]
Atenolol	Beta blocker	C07AB03; 75 mg C07CB03; 75 mg C07FB03; 75 mg	0.45
Bisoprolol	Beta blocker	C07AB07; 10 mg C07BB07; 5 mg	0.40
Citalopram	Antidepressant	N06AB04; 20 mg N06AB10; 10 mg	0.10
Fluoxetine	Antidepressant	N06AB03; 20 mg	0.08
Venlafaxine	Antidepressant	N06AX16; 100 mg	0.05
Losartan	Angiotensin II receptor antagonist	C09CA01; 50 mg C09DA01; 50 mg	0.04
Losartan carboxylic acid	Major metabolite of losartan	C09CA01; 50 mg C09DA01; 50 mg	0.06
Telmisartan	Angiotensin II receptor antagonist	C09CA07; 40 mg C09DA07; 80 mg	0.01
Valsartan	Angiotensin II receptor antagonist	C09CA03; 80 mg C09DA03; 120 mg C09DB01; 160 mg	0.10
Carbamazepine	Anticonvulsant	N03AF01; 1000 mg	0.05
Metformin	Antidiabetic	A10BA02; 2000 mg A10BD02; 2000 mg A10BD03; 2000 mg	0.60
Tramadol	Analgesic	N02AX02; 300 mg N02AX52; 150 mg	0.30

ATC Anatomical Therapeutic Chemical, *DDD* defined daily dose

[a] As defined by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHO 2012)

[b] From Baselt 2011 and PDR Network 2014

amount of active ingredient, as defined by the World Health Organization (WHO 2012), daily loads (in g/day) were calculated for each of the 11 pharmaceuticals and for each of the STP catchment areas. This is further called the predicted load (PL).

The measured concentrations of pharmaceuticals in influent sewage (in ng/L) were multiplied with the recorded flow rate (in L/day) and divided by a correction factor that takes into account the urinary excretion pattern of each pharmaceutical (Table 1) (Baselt 2011; PDR Network 2014). The resulting value is a daily load, expressed in grams/day, which is called the measured load (ML). The main purpose of this exercise is to compare the ML obtained experimentally with the theoretically calculated PL (Fig. 1). For losartan, two different MLs were calculated: one value derived from the parent compound and another value based on its major metabolite, losartan carboxylic acid.

Statistical analysis was executed with IBM SPSS Statistics 22 software (IBM, Armonk, USA), and $p<0.05$ was considered as statistically significant.

Results and discussion

Selection of the pharmaceuticals

Based on preliminary experiments and thorough literature search, information on the presence of the selected pharmaceuticals and their excretion pattern was obtained (Table 1). A rough estimation of the amount of people that use the selected pharmaceuticals was made by dividing the amount of DDDs prescribed in a specific STP catchment area with its corresponding total population number. This revealed that within 0.1 % (carbamazepine) to 2.0 % (metformin) of the population used the pharmaceuticals under investigation. In order to know if the substances under investigation had a stable use, the RSD (in %) of the monthly amount of DDDs prescribed for each of the 11 selected pharmaceuticals was calculated for a 1-year period for each of the five STP catchment areas (Table 2). The results showed a RSD <15 % in all cases and <10 % in 85 % of the cases. In general, these results support the assumption that the use of the selected pharmaceuticals is stable throughout the year which was a prerequisite for the study setup.

Predicted and measured loads

Figure 2 plots the mean PL versus the mean ML for each of the substances under investigation. Table 3 shows the detailed data on the PLs, MLs, and PL/ML ratio for all compounds and for all STP catchment areas. A related sample of Wilcoxon signed rank test (comparison of PL and ML for a specific STP catchment area and substance) revealed no statistically significant difference between PLs and MLs ($p=0.113$). However, this test does not give information on individual locations and/or substances.

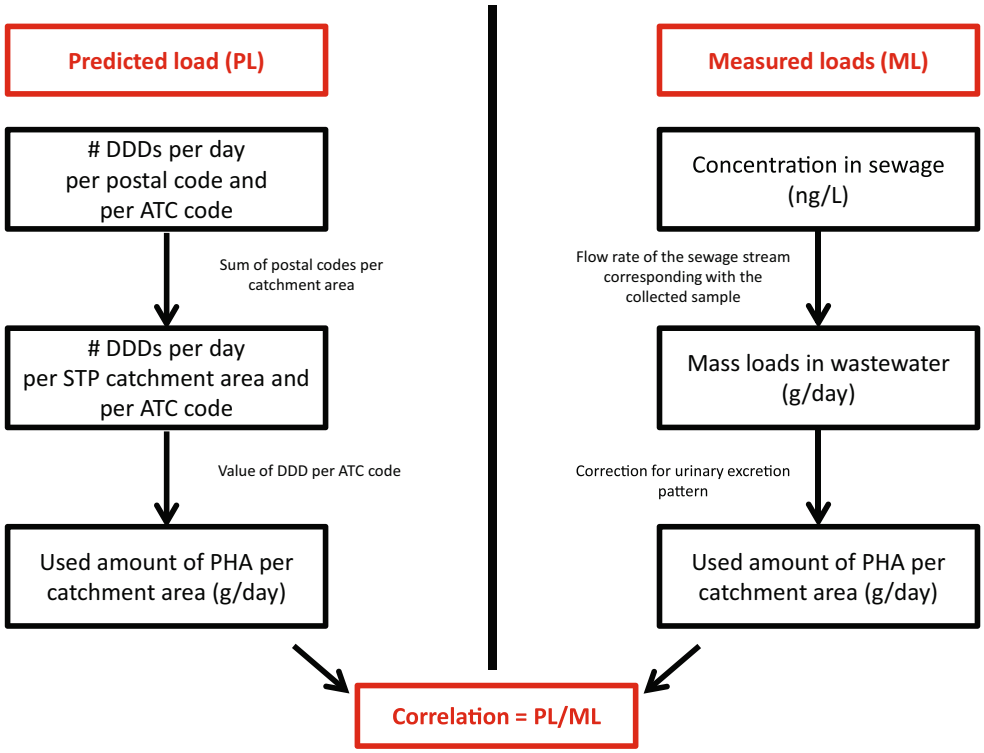

Fig. 1 Flow chart illustrating the calculations

Table 2 The relative standard deviation (in %) on the monthly prescribed DDDs for each of the 11 pharmaceuticals calculated on a period of 1 year per STP catchment area

	STP 1	STP 2	STP 3	STP 4	STP 5
Atenolol	5.6	11.8	6.1	9.8	7.3
Bisoprolol	5.9	5.8	6.2	5.5	4.2
Citalopram	6.0	7.0	6.0	5.0	7.0
Fluoxetine	6.7	10.0	7.4	13.6	7.1
Venlafaxine	6.2	10.3	7.2	6.8	5.1
Losartan	9.0	6.9	11.6	11.5	8.3
Telmisartan	7.1	7.2	10.4	8.7	7.7
Valsartan	8.5	9.7	10.8	9.0	6.7
Carbamazepine	5.1	12.0	8.6	5.0	8.2
Metformin	8.1	9.2	7.3	8.0	6.2
Tramadol	7.2	6.0	8.4	6.0	8.2

For 8 out of 12 substances, the relation between the PL and the ML is within the 3:1 or 1:3 range. Only for one pharmaceutical, bisoprolol, a relationship between PL and ML outside one order of magnitude was observed. It has to be furthermore noted that the PL/ML relationship for this compound was for all of the five STP catchment areas outside the 10:1 range; this means that the MLs of bisoprolol present a significant underestimation of its prescribed amounts. No clear explanation can be given for this observed discrepancy, but probably, further research into its stability in sewage is warranted. It has to be noted that ter Laak et al. (2014) found good correlations between PLs calculated from annual, national sales data and MLs from measured concentrations in surface water for other beta blockers, but bisoprolol was not investigated (ter Laak et al. 2014).

For telmisartan, the relationship between PL and ML is at the 1:10 border. This means that the MLs overestimate the actual consumption of this compound. A possible explanation for this observed difference can be found in the excretion pattern of this compound. Telmisartan is excreted in the urine unchanged only for 1 %, while it is for >95 % excreted via the feces (Stangier et al. 2000). Since no extensive research has been done to address the presence of pharmaceuticals in sewage water originating from fecal excretion, we only take the urinary excretion pattern into account in this study. In the case of telmisartan, however, this could lead to an underestimation of the applied correction factor because of the low urinary excretion coupled to a high fecal excretion. Further research into the influence of fecal excretion on the presence of compounds in sewage is necessary to have a better insight in this issue. The PL of losartan was compared with two different MLs: one originating from the presence of the parent compound in sewage and one from measured concentrations of its major metabolite, losartan carboxylic acid. The results reveal that the relationship of PL and ML calculated from losartan

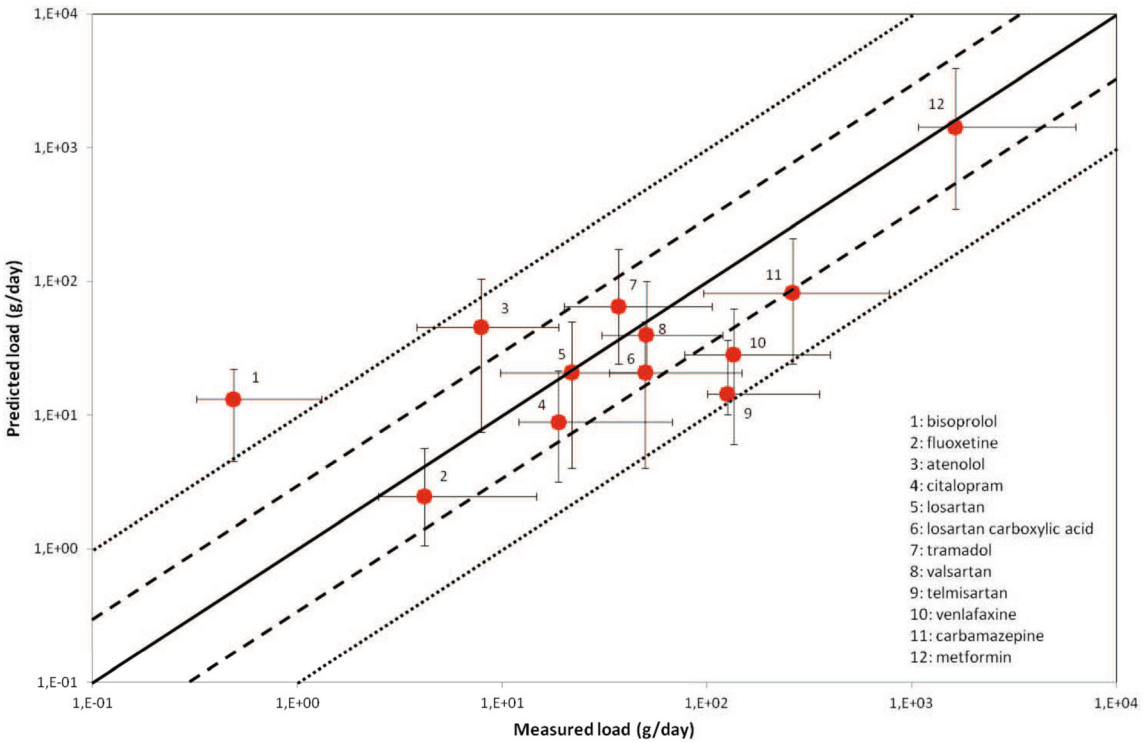

Fig. 2 Relationship between the predicted load and the measured load for the 12 investigated compounds. The *error bars* represent the minimum and maximum values of the five STP catchment areas investigated. The *solid line* represents a 1:1 relationship, the *dashed line* a 3:1 and 1:3 relationship, and the *dotted line* a 10:1 and 1:10 relationship

Table 3 Predicted load (PL), measured load (ML), and PL/ML ratio for each of the investigated pharmaceuticals per sewage treatment plant (STP) catchment area

		STP 1	STP 2	STP 3	STP 4	STP 5
Atenolol	ML (g/day)	8.86	4.06	11.06	9.58	5.85
	PL (g/day)	45.04	45.89	37.94	39.13	58.91
	PL/ML	5.09	11.30	3.43	4.08	10.07
Bisoprolol	ML (g/day)	0.64	0.32	0.49	0.83	0.16
	PL (g/day)	9.61	21.90	13.79	8.69	11.98
	PL/ML	15.08	68.73	28.26	10.48	72.80
Citalopram	ML (g/day)	7.65	14.87	49.11	15.55	6.75
	PL (g/day)	6.79	12.41	11.61	5.71	7.96
	PL/ML	0.89	0.83	0.24	0.37	1.18
Fluoxetine	ML (g/day)	1.68	4.25	10.57	2.07	2.26
	PL (g/day)	2.01	3.21	3.19	1.40	2.50
	PL/ML	1.20	0.76	0.30	0.68	1.11
Venlafaxine	ML (g/day)	57.44	102.80	264.06	160.50	90.86
	PL (g/day)	23.75	26.20	34.39	22.19	34.55
	PL/ML	0.41	0.25	0.13	0.14	0.38
Losartan	ML (g/day)	12.08	30.80	29.27	18.66	18.52
	PL (g/day)	16.76	28.93	18.17	18.29	21.84
	PL/ML	1.39	0.94	0.62	0.98	1.18
Losartan carboxylic acid	ML (g/day)	16.55	38.23	98.10	62.90	33.19
	PL (g/day)	16.76	28.93	18.17	18.29	21.84
	PL/ML	1.01	0.76	0.19	0.29	0.66
Telmisartan	ML (g/day)	25.50	229.39	227.64	35.25	113.57
	PL (g/day)	4.37	21.95	14.64	13.02	18.04
	PL/ML	0.17	0.10	0.06	0.37	0.16
Valsartan	ML (g/day)	20.13	68.82	65.04	37.95	61.23
	PL (g/day)	21.16	60.39	32.15	27.21	57.53
	PL/ML	1.05	0.88	0.49	0.72	0.94
Carbamazepine	ML (g/day)	173.65	268.47	511.21	166.72	195.22
	PL (g/day)	61.75	128.54	84.78	57.84	76.72
	PL/ML	0.36	0.48	0.17	0.35	0.39
Metformin	ML (g/day)	844.65	4689.23	1140.53	949.09	557.75
	PL (g/day)	1109.36	2487.25	1200.98	1083.93	1264.59
	PL/ML	1.31	0.53	1.05	1.14	2.27
Tramadol	ML (g/day)	17.00	52.39	68.94	22.53	24.09
	PL (g/day)	40.82	109.29	68.19	46.78	60.01
	PL/ML	2.40	2.09	0.99	2.08	2.49

concentrations are better than the calculations from losartan carboxylic acid.

The PLs and MLs were further evaluated by looking at their relative distribution around the mean of the five catchment areas under investigation. For this purpose, we divided the observed PLs and MLs in each catchment area by the mean PL and ML of the five catchment areas; this is defined as the relative PL or ML (Fig. 3). From these plots, there can be observed if the deviation from the mean is similar for the PL and ML. Relative PLs and MLs were generally in agreement, except for some cases. The inconsistent pattern observed for bisoprolol is probably linked with the abovementioned issue of the absolute correlation between PL and ML (Fig. 2). Furthermore, a significant higher relative ML compared to the relative PL was observed for 11 out of the 12 investigated substances in STP 3 catchment area. This suggests that this sewage contains a higher influx of pharmaceuticals than what would be expected from the prescription data. In this light, it could be that the presence of the 7th largest hospital in Flanders in this catchment area with approximately 1000 beds could lead to an extra influx of pharmaceuticals in the sewage, but this needs further research.

Only limited studies are available that investigate the correlation between the consumption of pharmaceuticals and

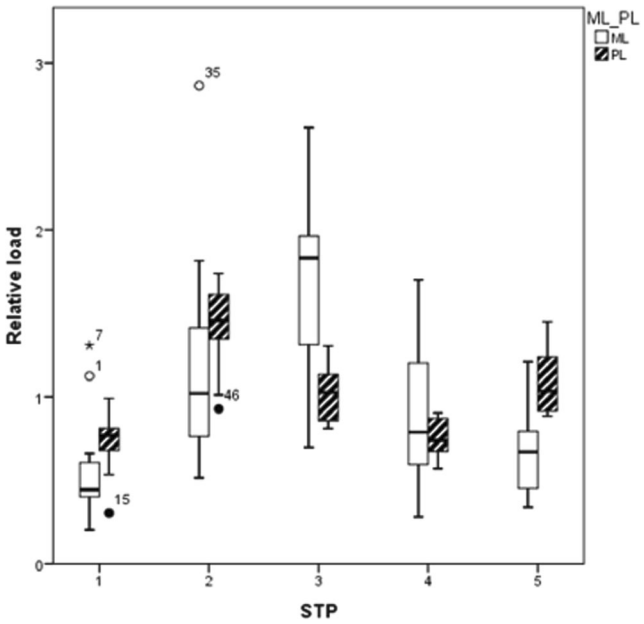

Fig. 3 Distribution of the PL and ML per STP catchment area around their mean (relative load=individual value of PL or ML divided by the mean (for the five STP catchment areas) of the PL or ML)

their presence in influent sewage (Carballa et al. 2008; Lai et al. 2011; Morasch et al. 2010; Tauxe-Wuersch et al. 2005; Verlicchi et al. 2014). However, often, these studies include pharmaceuticals that are subjective to large variations in consumption and also can be sold over the counter: antibiotics, analgesics, and anti-inflammatory drugs. For these compounds, it is thus difficult to reliably evaluate the relationship between PLs and MLs. Furthermore, these studies all use annual, national sales/prescription data to calculate the predicted loads, which are often not reflecting the local, daily use of pharmaceuticals. This study is, to the best of our knowledge, the first to evaluate the relationship between MLs and PLs in influent sewage with such detailed information to calculate PLs (i.e., from monthly amounts of DDDs prescribed per postal code). Some of the aforementioned studies also included substances with similar criteria as described in this manuscript. For example, the PL/ML ratio of carbamazepine in influent sewage was evaluated in three other studies. Variable results were observed, which is probably related with the large variability in the used correction factor for its excretion pattern (Carballa et al. 2008; Morasch et al. 2010; Verlicchi et al. 2014). Morasch et al. investigated the PL/ML ratio of four beta blockers (atenolol, metoprolol, propranolol, and sotalol) and three fibrates (bezafibrate, fenofibrate, and gemfibrozil) (Morasch et al. 2010). The results showed variable relationships within one class of pharmaceuticals, which is also reflected in the results from our study. Lai et al. observed good PL/ML relationships for atenolol, gabapentin, and hydrochlorothiazide while the PL/ML ratio of venlafaxine was only around 0.28 (Lai et al. 2011). This finding is comparable with the results for venlafaxine presented in this study and warrants further investigation.

Uncertainties

Figure 1 clearly illustrates that both calculations of PLs and MLs include several steps and that all are linked with a certain degree of uncertainty that can affect the precision of the observed relationship between PLs and MLs.

Uncertainties related with the predicted loads

The calculation of the PLs is made from the monthly amount of DDDs that are prescribed in the postal codes that correspond with the catchment area of a STP. Here, three sources of uncertainty can be found:

1. STP catchment areas are often not exactly corresponding with the boundaries of villages. Therefore, some assumptions have to be made with regard to which portion of a village is connected to the STP catchment area under investigation. Furthermore, it is also possible that not all households are connected to the sewage system.
2. The prescription data used in this study is provided based on the residence address of the patient. However, it is not clear which amount of the total urinary excretion of a user is ending up in the sewage of the catchment area that is linked with his/her residence address due to commuting.
3. The prescription data is available on a monthly time resolution only. To make a correlation between the MLs in a daily 24-h composite sample, the prescription numbers have to be transformed into daily data, which can introduce some uncertainty. However, as discussed in paragraph 3.1., no large variations are expected because of the properties of the selected pharmaceuticals.

Uncertainties related with the measured loads

The calculations of MLs from concentrations of pharmaceuticals in sewage are linked with several sources of uncertainties. However, it is important to note that the calculations in the present study do not rely on estimations of the amount of people that is served by a certain STP catchment area because of the availability of detailed prescription data per postal code. This is a large advantage of the present study compared with other studies since it is acknowledged in the literature that the estimation of the population that is served by a STP is still linked with large uncertainties because of inappropriate estimation methods (Castiglioni et al. 2013):

1. The sampling mode and sampling frequency can introduce errors in the measured concentrations because of

the possible losses of pulses of compounds of interest in sewage (Ort et al. 2010a, b). In this study, time-proportional sampling is applied with 10-min sampling intervals (144 subsamples pooled). Following a similar rationale as Castiglioni et al., we can assume that the uncertainty caused by the sampling procedure in this study is <15 % RSD (Castiglioni et al. 2013).

2. An important drawback of the presented data is that only a single 24-h composite sample per STP catchment area was used for the evaluation of PL/ML relationships. Therefore, we assume that the MLs of the selected pharmaceuticals are stable along days/weeks (this is suggested from the prescription data; see Table 2) and that samples under investigation had no anomalies.
3. Few to no information exist on the possible (bio)transformation of pharmaceuticals during the in-sewer transport from the place of excretion to the STP. This uncertainty can go two ways: a degradation of compounds would lead to an underestimation of MLs, while a formation would result in an overestimation. Experiments with illicit drugs have demonstrated that in-sewer (bio)transformation can have a severe influence for some compounds (van Nuijs et al. 2012).
4. The measurement of concentrations of pharmaceuticals in sewage with LC-MS/MS is obviously linked with an analytical uncertainty, which is often lower than 10 %. Although the applied analytical procedures are validated following official guidelines, we can only be sure of the quality of the methods through participating in large inter-laboratory exercises. These quality control schemes unfortunately do not exist to date.
5. Flow rate measurement systems have, comparable with analytical methods, a certain degree of uncertainty.
6. In order to estimate the use of pharmaceuticals from measured concentrations, knowledge about the pharmacokinetics (bioavailability, metabolism, and excretion pattern) of a pharmaceutical is imperative. The use of one (mean) value that reflects the excretion pattern of a pharmaceutical introduces an additional uncertainty because of the sometimes large differences observed between studies, inter-individual variations, urinary vs fecal excretion, etc. Furthermore, it has to be noted that pharmaceuticals with a small correction factor (e.g., telmisartan) are prone to larger uncertainties.
7. If pharmaceuticals are disposed unused in the sewer system or if the substances are subject to illegal trade and use, a skewed PL/ML relationship can be expected. Also, not all prescribed pharmaceuticals are used by the patients, and thus, only a proportion is released to the sewage system (Boxall et al. 2014).

Clearly, the high number of possible sources of uncertainties indicates that the approach is heavily reliant on the availability of good quality prescription and monitoring data. Also, the approach cannot be applied to non-prescription pharmaceuticals or for compounds for which monitoring data do not exist.

Conclusions

This study is, to the best of our knowledge, the first to use this detailed prescription data to calculate PLs and to compare them with MLs from 11 pharmaceuticals in influent sewage. The results reveal for all but one (bisoprolol) pharmaceutical a relationship between PL and ML within one order of magnitude and for more than 60 % of the substances within the 3:1 or 1:3 ratio. Furthermore, important uncertainties in evaluating PL/ML ratios are highlighted, e.g., the use of only one sample per STP catchment area in this study can introduce a large uncertainty. In order to execute SBE studies, one must take care that all necessary information is available regarding sewage sampling, stability of substances in sewage, pharmacokinetics, and analytical performance. Only then estimations of (illicit) drug and pharmaceutical use via the SBE approach can be made in a sound and reliable way.

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