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PRESENCE OF PHARMACEUTICS IN WASTEWATER FROM WASTE WATER TREATMENT PLANT "ZABRZE – ŚRÓDMIEŚCIE" IN POLAND

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OBECNOŚĆ FARMACEUTYKÓW W ŚCIEKACH POCHODZĄCYCH Z POLSKIEJ OCZYSZCZALNI ŚCIEKÓW „ZABRZE – ŚRÓDMIEŚCIE"

Niniejszy artykuł przedstawia wyniki badań ścieków surowych pochodzących z miejskiej oczyszczalni ścieków „Zabrze – Śródmieście". Ścieki surowe analizowane były pod kątem zawartości w nich pozostałości 30 farmaceutyków i ich metabolitów oraz 2 substancji zapachowych. Wybrane do badań farmaceutyki ze względu na swoje właściwości i obszar działania klasyfikowane są jako: środki cieniujące (stosowane podczas prześwietleń, tzw. „środki kontrastujące"), antybiotyki, regulatory tłuszczu, leki przeciwbólowe i przeciwzapalne, leki antyepileptyczne oraz leki stosowane w leczeniu psychiatrycznym. Przeprowadzone badania wykazały w próbkach ścieków obecność 20 z 32 wytypowanych do badań substancji, w stężeniu powyżej ich limitu wykrywalności. Najwyższe stężenie w ściekach osiągnął iopromid, związek zaliczany do środków cieniujących. Jego maksymalne stężenie wynosiło 27,0 μg/dm^3. Inne leki, takie jak: iopamidol, iomeprol, diatrizoat, iohexol, sulfametoksazol, karbamazepina, ibuprofen, ibuprofen-OH, naproksen, diklofenak, bezafibrat, ketoprofen oraz galaksoid (substancja zapachowa), obecne były w ściekach, w maksymalnych stężeniach od 1,0 μg/dm^3 (bezafibrat) do 13,0 μg/dm^3 (iomeprol). Leki gemfibrozil i indometacyna oznaczane były w ściekach w stężeniach maksymalnych 0,22 μg/dm^3 (gemfibrozil) i 0,42 μg/dm^3 (indometacyna). Na podstawie danych literaturowych wiadomo, iż wybrane przez nas do badań leki nie są całkowicie eliminowane ze ścieków w procesach biologicznego oczyszczania. Wraz ze ściekami oczyszczonymi przedostają się do odbiorników wodnych. Pozostałości po farmaceutykach są w dalszym ciągu substancjami czynnymi biologicznie, mają zdolność do akumulacji w środowisku lub w tkankach organizmów żywych. W literaturze światowej wciąż brakuje publikacji na temat ekotoksycznych zagrożeń wynikających z obecności farmaceutyków w środowisku, a informacje dotyczące pozaustrojowego rozkładu farmaceutyków są bardzo lakoniczne.

Summary

This article describes monitoring results of raw wastewater from one Polish municipal wastewater treatment plant (WWTP). The residues of 30 pharmaceutics belonging to particular drugs classes such as contrast media, antibiotics, lipids regulators, antiphologistics, psychiatric and anticpileptic agents, drug's

metabolites and 2 musk compounds have been investigated. The investigation showed occurrence of 20 out of 32 selected compounds above their limit of detection. Iopromide, a compound belonging to contrast media, was noticed at the highest concentration. The concentration of this compound in WWTP-influent was equaled to 27.0 μg/dm³. Other drugs, such as, like iopamidol, iomeprol, diatrizoat, iohexol, sulfomethoxazole, carbamazepine, ibuprofen, ibuprofen-OH, naproxen, diclofenac, bezafibrate, ketoprofen, and musk compound – galaxolide were detected at maximum concentration between 1.0 μg/dm³ (bezafibrate) and 13.0 μg/dm³ (iomeprol). The acidic compounds such as gemfibrozil and indomethacin were determined above their limit of detection, with concentration up to 0.22 μg/dm³ and 0.42 μg/dm³, respectively. Based on the literature data, the above-mentioned drugs are not completely removed from sewage during treatment processes and with effluent from WWTP they are introduced to receiving waters. Due to their chemical properties, residues of pharmaceutics may persist in the environment and the present knowledge about their ecotoxicological effects is insufficient.

INTRODUCTION

First information about drugs occurrence in aquatic environment in Europe appeared in the 1980s. Investigations in the United Kindom revealed presence of a few medicines at the concentrations up to 1 μg/dm³, but precise quantification of single drugs was not always possible [14, 15]. With the progress of analytical methods new facts about the problems concerning persistence of medical substances in wastewaters, rivers, streams and ground waters appeared. In the second half of the 1990s, the occurrence of 32 different drugs residues and additionally 18 antibiotics has been detected in German WWTP-effluents, rivers and stream waters [7, 12]. Also endocrine disruptors and anti-tumor agents were detected in sewage of German hospitals and in municipal wastewater [6, 12].

In Poland until 1999, no data about the pharmaceutics occurrence in the aquatic environment were available. In 1999 and 2000, the concentrations of selected compounds in municipal sewage were calculated basing on the data from Drug Institute in Warsaw concerning the amount of annual sales and drugs consumed in Poland [4]. The consumption of pharmaceutics in Poland is presented in Table 1.

Table 1. Consumption of selected drugs in Poland, results from 1999–2000 [4]

Drug	Categories of drugs	Consumption in 1999 [Mg]	Consumption in 2000 [Mg]
Bezafibrate	lipid regulator	1.40	0.83
Carbamazepine	antiepilepileptic	41.58	41.36
Diazepam	psychiatric drug	0.77	0.50
Diclofenac	antiphlogistic	18.89	20.88
Ethinylestradiol	hormone	0.01	0.01
Ibuprofen	antiphlogistic	44.64	58.58
Iopromide	contrast medium	11.42	10.10
Roxitromicine	antibiotic	2.20	2.04
Sulfamethoxazole	antibiotic	37.07	31.99

In order to evaluate the concentrations of a particular drug in municipal sewage, the annual amount of the consummated drug was multiplied by the percentage of an unchanged form of the excreted drug, and then the obtained value was compared with the total amount of municipal sewage in Poland. The calculated concentrations of a selected drug in municipal wastewaters in Poland, in 1999 and 2000 are presented in Table 2.

Table 2. Estimated concentration of selected drugs in wastewaters in Poland, results from 1999 and 2000 [4]

Drug	1999 [$\mu g/dm^3$]	2000 [$\mu g/dm^3$]
Bezafibrate	0.44	0.28
Carbamazepine	0.52	0.55
Diazepam	0.015	0.010
Diclofenac	0.24–1.78	0.28–2.1
Ethinylestradiol	0.0024	0.0027
Ibuprofen	2.81	3.90
Iopromide	7.18	6.76
Roxitromicine	0.76	0.75
Sulfamethoxazole	4.66	3.21

The obtained results are approximate but they indicate that problem of drugs occurrence in the environment concerns Poland, too. In the selected group of pharmaceutics, the highest calculated concentrations were recorded for iopromide (7.18 $\mu g/dm^3$) and sulfamethoxazole (4.66 $\mu g/dm^3$) in 1999. Sulfamethoxazole is a component of a very popular medicine, "Biseptol" and application level of "Biseptol" in Poland is very high. However, not only consumption is responsible for concentration of drugs residues in sewage. These concentrations depend on the drugs' pharmacokinetical behavior. Iopromide (iodine, non-ioned X-ray contrast medium), which is not metabolized in a human body, can serve as an example.

In 2000, the Environmental Biotechnology Department of SUT (Poland) in co-operation with German Institute for Water Research and Water Technology (ESWE) executed investigations of raw wastewaters in Zabrze, Poland. The presentation of the results of preceding investigations is the aim of this publication.

MATERIALS AND METHODS

Sampling procedure

Raw wastewaters used for the tests were taken from an influent to biological stage of WWTP in Zabrze (max flow 63 000 m^3/d). The grab samples were taken in six sampling series – three of them in winter periods (02.2002 – 03.2002) and the rest of them in summer period (07.2002 – 08.2002). All of the samples were taken on weekdays. The samples for the analysis were frozen and stored in dark-glass bottles at -18°C. The frozen samples were transported to

ESWE-Institute in Germany. All wastewater samples were than analyzed using GC/MS or LC/MS/MS methods, respectively.

Analytical methods

The selected drugs residues were determined using several mulit-methods described by Ternes, Hirsch, Heberer and Sacher [5, 7, 8, 11–13]. All wastewater samples were filtered using glass fiber (< 1 μm). The methods applied solid-phase extraction (SPE) with reversed-phase octadecyl adsorbents for extraction of selected drugs (or groups of drugs) from wastewater samples. The neutral drugs, except from carbamazepine, were determined by GC/MS without any derivatization. The X-ray contrast media and antibiotics, after solid phase extraction (SPE), were detected by LC/MS/MS methods. The acidic drugs were quantified and confirmed by GC/MS after solid phase extraction (SPE) and methylation by diazomethane. The limits of detection for the pharmaceutics were between 0.01 μg/dm^3 and 0.25 μg/dm^3. It depended on the individual compound property, the sample volume and the sample matrix [3].

RESULTS AND DISCUSSION

WWTP in Zabrze is localized in the most populated region in Poland (Upper Silesia). It is typical municipal WWTP where wastewaters from domestic, industrial and hospital discharges (more then 0.5% of max flow) are treated. Sewage samples were taken from influent to biological part of this plant.

X-ray contrast media

Residual amounts of contrast media can reach municipal wastewater from hospital discharge of diagnostic departments. Only in Berlin, about 15 Mg of organic, iodine contrast media are used each year [17]. In Poland the application level of only one contrast medium – iopromide is as high as 10 Mg per year [4].

Six out of the seven selected contrast media (five compounds and their two metabolites) were detected in WWTP-influent. Iopromide reached a maximum concentration as high as 27.0 μg/dm^3, with a 90-percentile of 25.0 μg/dm^3. The median concentration for iopromide in raw wastewater samples was 13.3 μg/dm^3. The concentration of iopromide is so high because this compound is not metabolized in the human body and it is excreted in an unchanged form with urine. Concentrations of X-ray contrast media in sewage are depended on the amount of work done in hospital diagnostic departments – generally, concentrations of contrast media dramatically increased on weekdays, because X-ray sessions are performed predominately from Monday to Friday. For the rest of selected contrast media, such as: iopamidol, iomeprol, diatrizoat and iohexol, the median values did not exceed 1.34 μg/dm^3. The metabolite of contrast media, ATH, was not detected in investigated wastewater samples. Metabolite DAMI was detected with concentration up to 0.49 μg/dm^3. The analytical data are listed in Table 3.

Table 3. Concentrations of contrast media and their metabolites

Drug	LOD*	Number of samples	n > LOD	Median [μg/dm^3]	90-percentile	Maximum [μg/dm^3]
Iopamidol	0.01	6	5	0.22	2.10	2.20
Iopromide	0.01	6	5	13.30	25.00	27.00
Iomeprol	0.01	6	5	1.34	8.05	13.00
Diatrizoat	0.01	6	4	1.16	4.20	6.90
Iohexol	0.01	6	5	0.24	3.12	5.80
DAMI	0.01	6	3	0.13	0.45	0.49
ATH	0.01	6	n.d.	n.d.	n.d.	n.d.

*LOD – limit of detection [μg/dm^3], n.d. – not detectable

Antibiotics

Two antibiotics, sulfomethazin and sulfamethoxazole, were detected in the experimental session. Sulfamethoxazole, an antibiotic belonging to sulfonamides, an ingredient of a very popular in Poland drug called "Biseptol", was present in all investigated raw wastewater samples. Its maximum concentration was as high as 2.0 μg/dm^3 and the median value concentration was 1.55 μg/dm^3. Sulfomethazin, another sulfonamide compound, was not detected in any raw wastewater samples (Table 4.).

Table 4. Concentration of selected antibiotics

Drug	LOD*	Number of samples	n > LOD	Median [μg/dm^3]	90-percentile	Maximum [μg/dm^3]
Sulfomethazin	0.02	6	n.d.	n.d.	n.d.	n.d.
Sulfamethoxazole	0.02	6	6	1.55	1.85	2.00

*LOD – limit of detection [μg/dm^3], n.d. – not detectable

Neutral drugs

The definition "neutral drugs" is applied for different compounds belonging to selected medicinal classes which contain no acidic functional groups. They can be enriched at neutral pH in the reserved phase and sorbents can be analyzed by GC/MS without derivatization [11].

In the group of eleven investigated neutral drugs only three (pentoxifylline, phenazon and carbamazepine) were detected in WWTP-influent. Pentoxifylline, a vasodilator agent, showed a median value concentration of 0.44 μg/dm^3 and 90-percentile of 0.67 μg/dm^3 in WWTP-influent. Its maximum concentration in investigated wastewater samples was up to 0.68 μg/dm^3. Phenazon, an antiphlogistic drug, was present in all wastewater samples with the maximum concentration of 0.18 μg/dm^3.

Carbamazepine is an antiepileptic drug. Only 1–2% of this drug is excreted from the human body in a non-metabolized form. Consumption of carbamazepine in Europe is very large. For example, in Poland annual scale of this compound exceed 40 Mg per year, in Germany – approximate by 80 Mg per year [13] and in the Austria annual amount of carbamazepine sold and consumed exceeds 6 Mg [1]. German investigations showed that carbamazepine is almost not removed from wastewaters during treatment processes at the WWTP. Only 7% of this drug was removed in the WWTP. The presence of carbamazepine in German WWTP-influents, effluents and river water was detected by Ternes [12]. Carbamazepine was present in all investigated wastewaters samples at the maximum concentration of 1.6 μg/dm^3 and the median value 1.15 mg/dm^3.

Other neutral drugs such as ifosfamide and cyclophosphamide were not detected in any investigated sewage samples. Both of these medicines are antineoplastic agents which they are applied frequently in cancer chemotherapy. An Oncological Centre is localized in Gliwice, about 10 km from Zabrze. The wastewaters from oncological hospital do not feed the investigated WWTP in Zabrze. Hospital sewage gets into WWTP in Gliwice and in this sewage a presence of ifosfamide and cyclophosphamide can be expected. Results of neutral drugs monitoring are listed in Table 5.

Table 5. Concentration of selected neutral drugs and musk compounds

Drug	LOD*	Number of samples	n > LOD	Median [μg/dm^3]	90 - percentile	Maximum [μg/dm^3]
Pentoxifylline	0.10	6	6	0.44	0.67	0.68
Phenazon	0.10	6	1	< LOD	0.09/< LOD	0.18
Ifosfamid	0.01	6	n.d.	n.d.	n.d.	n.d..
Cyclophosphamide	0.01	6	n.d.	n.d.	n.d.	n.d.
Carbamazepine	0.05	6	6	1.15	1.55	1.60
Dimethyloaminophenazon	0.10	6	n.d.	n.d.	n.d.	n.d.
Etofibrate	0.10	6	n.d.	n.d.	n.d.	n.d.
Diazepam	0.03	6	n.d.	n.d.	n.d.	n.d.
Propyphenazon	0.10	6	n.d.	n.d.	n.d.	n.d.
Coffein	0.05	6	n.d.	n.d.	n.d.	n.d.
Gilbenclamid	0.05	6	n.d.	n.d.	n.d.	n.d.
Galaxolide (musk)	0.10	6	6	0.61	1.02	1.20
Tonalide (musk)	0.10	6	n.d.	n.d.	n.d.	n.d.

*LOD – limit of detection [μg/dm^3], n.d. – not detectable

Musk compounds

Polycyclic musk compounds such as galaxolide and tonalide can reach municipal sewage with residues of fragrance substances. These perfumes components may be accumulated in the human fat tissues and human milk – they enter the body through the skin. Basing on the survey conducted by Zehinger and Herrmann [16] concentration of galaxolide in human milk was observed in 73 μg/kg fat from milk and tonalide in 74 μg/kg fat from milk.

In investigated wastewater samples tonalide was not detectable above the limit of detection, but galaxolide was present in all samples with the maximum concentration of 1.2 μg/dm^3. Median value concentration of this compound exceeded μg/dm^3 (Table 5).

Acidic drugs

The term "acidic drugs" defines pharmaceutical compounds containing carboxylic groups and one or two phenolic hydroxy groups [11]. All of these compounds can be determined at pH 2–3. The selected acidic pharmaceutics belong to different medicinal classes, for example antiphlogistics and lipid regulator agents.

In raw wastewater samples six acidic antiphlogistics were detected, such as: naproxen, ibuprofen, ibuprofen-OH (one from its principal metabolites), diclofenac, indomethacin and ketoprofen and three acidic lipid regulator agents (bezafibrate, gemfibrozil and clofibric acid – a metabolite of lipid regulator drugs).

Naproxen was present at concentrations varying between 2.7–8.4 μg/dm^3. Its concentration was the highest concentration of all detected acidic drugs. So high concentration of this compound in wastewater can be explained by the fact that naproxen is applied not only to humans – appreciable amounts are used in veterinary medicine, too. Other drugs such as ibuprofen and one of its major metabolites ibuprofen-OH, were detected in raw wastewater samples at the maximum concentrations of 2.8 μg/dm^3 and 5.1 μg/dm^3, respectively. Ibuprofen is quite well removed during wastewater treatment but the data about removal-rate of ibuprofen-OH in WWTP are different [2, 9]. Buser observed an efficient removal of ibuprofen and ibuprofen-OH (96–99.9%) during wastewater treatment [2], whereas Stumpf reported a significant elimination of ibuprofen but no elimination of ibuprofen-OH [9].

In 2000 approximately 21 Mg of diclofenac were prescribed in Poland. A real consumption of this compound is much higher because this drug can be purchased also as an over the counter drug. Removal-rate of diclofenac during wastewater treatment is located in interval-range 17–69% [10, 12]. Diclofenac was detected in all investigated sewage samples at the maximum concentration of 2.0 μg/dm^3 and the median-value of 1.75 μg/dm^3. This drug was detected in German and Austrian raw wastewater at the similar concentration range [1, 12].

Other antiphologistic drugs – indomethacin and ketoprofen – were present in raw wastewater samples with the maximum concentrations of 0.4 and 2.3 μg/dm^3, respectively.

Lipid regulator agent – bezafibrate was present in all investigated wastewater samples with the maximum concentration of 1.0 μg/dm^3. Another lipid regulator agent – gemfibrozil was detected in five out of six wastewater samples with the maximum concentration of 0.22 μg/dm^3. Both of these compounds were present in most of German WWTP-influents and effluents investigated by Ternes [12]. Clofibric acid, the active metabolite of few lipid regulators, was detected in several investigations of municipal WWTP influents and effluents

[1, 10, 12]. In the wastewater samples clofibric acid was identified only in one out of six samples (Table 6.).

Table 6. Concentrations of selected acidic drugs

Drug	LOD*	Number of samples	n > LOD	Median [μg/dm^3]	90-percentile	Maximum [μg/dm^3]
Fenoprofen	0.05	6	n.d.	n.d.	n.d.	n.d.
Ibuprofen-OH	0.05	6	6	3.40	4.80	5.10
Clofibrinic acid	0.05	6	1	<LOD	<LOD	0.08
Ibuprofen	0.05	6	6	2.25	2.60	2.80
Naproxen	0.05	6	6	6.15	7.95	8.40
Diclofenac	0.05	6	6	1.75	2.00	2.00
Gemfibrozil	0.05	6	5	0.14	0.21	0.22
Indomethacin	0.05	6	6	0.23	0.36	0.42
Bezafibrate	0.25	6	6	0.78	0.96	1.00
Ketoprofen	0.05	6	6	1.95	2.20	2.30

*LOD – limit of detection [μg/dm^3], n.d. – not detectable

CONCLUSIONS

German investigations showed that residues of drugs in municipal sewage are incompletely removed during conventional wastewater treatment [6, 12]. Their occurrence in raw wastewater may indicate that they may be present in treated wastewater, too. They may get through into surface waters with WWTP-effluents. Some compounds such as an antiepileptic drug – carbamazepine or residue of fragrance agent – galaxolide may be accumulated in human and animal bodies and their long-term effects for organisms are not completely known. Both of these compounds were detected in all raw wastewater samples and they are expected in Polish treated wastewater. Residual antibiotics in aquatic environment may provoke formation of antibiotic resistance bacteria because in many cases the genetic code for antibiotic resistance is placed on so-called R-plasmids, which can be transferred between bacteria. Residue of sulfomethoxazole was observed in all investigated wastewater samples. Non-biodegradable residues of X-ray contrast media, by conjugation with other inorganic compounds, for instance heavy metals, may provoke toxic effects for micro- and macro- organisms. Most of these compounds are present in the wastewater samples with concentrations up to 27.0 μg/dm^3 (iopromide). Residues of some acidic drugs were present in all investigated wastewaters samples. Naproxen, an antiphologistic drug, was identified with maximal concentration of 8.4 μg/dm^3. The average concentration of

naproxen in Polish raw wastewater was as high as 5.98 μg/dm³ and with comparison to German and Austrian results this concentration is significantly higher. The average concentrations of naproxen in raw wastewaters in Germany and Austria were 1.3 μg/dm³ and 0.93 μg/dm³, respectively. Lipid regulator agent, bezafibrate, was also present in all investigated wastewater samples. Its average concentration was 0.71 mg/dm³. This concentration is relatively low with comparison to results from other European countries [1, 12]. For instance, average concentration of bezafibrate in raw wastewater in Germany was 5.6 μg/dm³ and in wastewaters in Austria 2.2 μg/dm³ (Table 7).

Table 7. Comparison of average concentrations of selected drugs in raw wastewaters in Poland, Germany and Austria

Drug	Poland [μg/dm³]	Germany [μg/dm³]	Austria [μg/dm³]
Bezafibrate	0.71	5.6	2.20
Diclofenac	1.70	1.9	0.54
Ibuprofen	2.25	4.4	0.77
Naproxen	5.98	1.3	0.93

The concentration of drug residues and their metabolites in wastewaters in different regions and the country varies but the problem is common for all Europe. A creation of new technologies to remove residues of pharmaceuticals from wastewaters is necessary. Studies of environmental risk assessment and fate of drugs in the environment are of great importance.

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