POST CONFERENCE WORKSHOP

PHARMACEUTICAL RESIDUES: PARENT COMPOUNDS, METABOLITES AND TRANSFORMATION PRODUCTS AS ENVIRONMENTAL CONTAMINANTS

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Pharmaceutical residues: parent compounds, metabolites and transformation products as environmental contaminants
5 June, 2013, Hotel Atria Nîmes, France

Workshop chaired by

Ester Heath (Jožef Stefan Institute, Ljubljana, Slovenia)

PROGRAM

09.00 Chairman's welcome and opening remarks

09:10 *Study of the reactivity of cytostatics in water with free chlorine by ultra performance liquid chromatography - hybrid quadrupole-Orbitrap - tandem mass spectrometry*
Noelia Negreira, IDAEA-CSIC, Girona, Spain

09:30 *Formation of stable transformation products of pharmaceuticals in the water treatment processing.*
Jana Weiss, IVM, Amsterdam University, The Netherland

09:50 *Transformation of the anticonvulsant lamotrigine in the aquatic environment.*
Sandra Perez, IDAEA-CSIC, Girona, Spain

10:10 MORNING COFFEE

10:40 *Enzymatic degradation of tetracycline and generation of transformation products.*
Marta Llorca, Catalan Institute for Water Research-ICRA, Girona, Spain

11:00 *Cytostatics in the environment: analysis and occurrence.*
Ester Heath, Jozef Stefan Institute, Slovenia

11:20 *Multi-analyte determination of 26 cytostatics and metabolites by liquid chromatography-electrospray-tandem mass spectrometry: optimization, analytical performance, and study of the stability and optimum storage conditions for their determination in wastewater.*
Miren Lopez de Alda, IDAEA-CSIC, Girona, Spain

11:40 *Identification of ozonation and chlorination by-products of ciprofloxacin by analysis by LC/HR-MS.*
Véronique Boireau, Veolia Environnement Recherche et Innovation, France

12.00 *Identifications of phototransformation products of antiviral zanamivir with HILIC-LTQ-Orbitrap-MS in aqueous matrices.*
Bozo Zonja, IDAEA-CSIC, Girona, Spain

12:20 *Degradation and transformation of 5-fluorouracil and capecitabine*.
Tina Kosjek, Jozef Stefan Institute, Slovenia

12:40 Discussion and final Remarks

13:00 End of Workshop

13:15 LUNCH

ABSTRACTS

Study of the reactivity of cytostatics in water with free chlorine by ultra performance liquid chromatography - hybrid quadrupole-Orbitrap - tandem mass spectrometry

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Cytostatics are a major class of chemotherapeutic drugs with great potential to cause genotoxic and/or mutagenic effects [1]. They are mainly discharged in the aquatic media through excretion from patients under medical treatment. In fact, some of them have been detected in hospital wastewaters at concentrations varying from ng/L to µg/L [2]. Notwithstanding this, the number of studies reporting the presence of these compounds in water is still scarce. This fact may be attributed to either a low medical use or, more likely, to the existence of degradation processes in the aqueous medium leading to their transformation into other products, which may be even more toxic and persistent than the original ones. Little information is known in this respect. Recently, Araceli et al. [3] investigated the aqueous degradation by ozone of two cytostatics, cyclophosphamide and methotrexate, by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Their results show a slow degradation for cyclophosphamide, whereas methotrexate reacted quickly with molecular ozone at doses typically applied in drinking water treatment. However, identification of the generated by-products was not carried out.

On the other hand, chlorine can be also employed to improve the efficiency of sewage plants; thus, compounds surviving to primary and biological treatments might get in contact with this oxidant when used in tertiary treatments. As a result, pollutants might evolve into new species with a different persistence and toxicity than their precursors. In this way, it has been demonstrated that several pharmaceuticals show favourable chlorination rates rendering halogenated by-products [4]. However, to the best of our knowledge, the stability of cytostatics in the presence of free chlorine has not been yet investigated. In this work, various selected cytostatics have been studied for their stability in chlorinated water, and the transformation products formed have been tentatively identified. The experiments have been conducted at different pHs (from 6 to 8), with free chlorine and analytes at concentrations in the range of µg/mL and ng/mL, respectively. Analysis of the parent species and transformation products has been carried out by ultra performance UPLC-MS/MS with a Q Exactive hybrid quadrupole-Orbitrap mass spectrometer.

Acknowledgements

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Formation of stable transformation products of pharmaceuticals in the water treatment processing

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Risk assessment of pharmaceutical products in the environment is currently covered by high uncertainties, due to, on the one hand, the lack of data (in particular of long term exposure and toxicity) and, on the other hand, the lack of consideration of additional parameters such as the exposure to mixtures and the presence of metabolite and/or transformation products (TPs). After human consumption, pharmaceutically active substances can be excreted and enter the effluent treatment facilities. Often degradation in sewage and water treatment and the environment is incomplete, resulting in the formation of stable transformation products. In only a few cases, full mineralization of the parent compounds is achieved. This is even more important as advanced techniques employing e.g. ozone, chlorination, and photodegradation, are subject of discussion for the removal of pharmaceuticals in effluent and drinking water treatment. Treatments using these techniques may even lead to the formation of transformation products that may be more toxic than the parent compound. The formation and presence of such TPs in the effluent of sewage works, surface water, and drinking water treatment is reported in the scientific literature with increasing frequency.

The Pharmas project (www.pharmas-eu.org, EU grant agreement no. 265346) has been funded to assess the ecological and human health risks posed by exposure to a selection of pharmaceuticals focusing on a poorly investigated compound group, i.e. the anticancer drugs and their transformation products (TPs) arising from water treatment. The compounds selected and reported here are 5-FU, Imatinib and Cyclophosphamide. The formation of stable transformation products was investigated in various stages of the water treatment cycle (both drinking and sewage) in laboratory scale studies. Treatment processes investigated are chlorination, ozonation and UV-disinfection for drinking water treatment and also biodegradation in combination with photodegradation for sewage treatment. For lab-scale experiments, the initial concentration of each standard solution was 1 mg/L in order to be able to identify possible TPs. The chlorine added was chosen to ensure a molar ratio target:chlorine of 1:100. Photodegradation was done with a Xenon lamp and the biodegradation testing covered 28 days. For structure elucidation of the stable transformation products formed, LC-TOF/MS with electrospray ionization (ESI) analysis were performed in both positive and negative mode. The accurate masses were used for the identification of the transformation products using MetaboliteDetect and DataAnalysis software (Bruker Daltonics).

The knowledge on specific transformation product formation pathways, the molecular identity and (eco)toxicological behavior is expected to ultimately lead to recommendations for the targeted design of pharmaceuticals with improved degradation and elimination properties, whilst maintaining their therapeutic value.

Transformation of the anticonvulsant lamotrigine in the aquatic environment

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No more than 8% of the marketed pharmaceuticals have been monitored in the environment and only few of their human metabolites and transformation products have been included in current methods for trace analysis of pharmaceuticals. One of the pharmaceuticals which has received little attention regarding its presence in the aquatic environment is lamotrigine, an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. This pharmaceutical is extensively metabolized in humans to produce predominantly the N2-glucuronide and to a minor extent the N2-methyl-lamotrigine1. There are no reported findings about its transformation in the aquatic environment. Only, one U.S. study revealed the environmental occurrence of lamotrigine and its N2-glucuronide with mean concentrations in wastewater of 488 and 209 ng/L, respectively2. Less frequent detection in surface waters went along with occasional positive findings in groundwater samples.

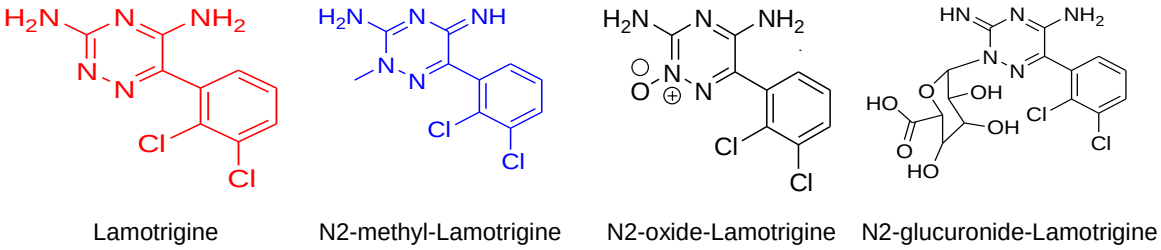

Figure 1. Structures of Lamotrigine, its metabolites and its TP

In order to investigate the biotic and abiotic transformations of lamotrigine, we designed two experiments: one for assessing its potential biodegradation by the bacterial community in mixed liquor from a municipal STP and the other in order to assess its photodegradability using a Suntest simulator. While the UPLC analysis of the samples from the aerated batch-reactor showed the formation of a single metabolite, the photolysis provided three TPs. High resolution mass spectrometry ((+)ESI-LTQ-Orbitrap) allowed to propose the structures of the four detected TPs with ion masses of m/z 219.0312, 237.0417 and 273.0184 Da for photolysis and of m/z 269.0235 Da for biodegradation. Their formation was the result of two principal reactions: (a) dechlorination of the aromatic ring and subsequent substitution of the halogen by a hydroxyl group and (b) N-methylation in the position two of the triazine ring.

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Enzymatic degradation of tetracycline and generation of transformation products

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Tetracycline is a broad-spectrum polyketide antibiotic indicated for use against many human and veterinary bacterial infections such as urinary tract infections and acne among others. This antibiotic is consumed through oral, topical (skin and eye), intramuscular or intravenous application. Since this compound is hardly metabolized, tetracycline is eliminated from the body via fecal and renal excretions reaching waste water treatment plants (WWTP). Although the elimination/redistribution of this compound in WWTPs is between 60 and 70% (Gros et al. 2010), tetracycline is still present in effluents discharged into the river at low ng/L. The presence of traces of antibiotics (and pharmaceuticals in general) in the environment can induce the development of antibiotic-resistant pathogens, causing problems in biota and for human health (Hirsch et al. 1999; Bautitz et al. 2007). In this context, the evaluation of alternative treatments for its elimination should be considered such as enzymatic processes. This work is based in a novel enzymatic degradation process (de Gunzburg et al. 2012) - with 0.01 g/L of free Laccase enzyme from Trametes versicolor.

The main results outline elimination between 24 and 30% after 24 h of exposure. The possible transformation products generated during degradation process by enzymes have been studied by liquid chromatography coupled to a hybrid high resolution mass spectrometer LTQ-Orbitrap Velos (Thermo Fisher Scientific). Different sample pretreatment methods have been evaluated such as the novel on-line turbulent flow chromatography in order to remove potential matrix effects of the matrix as well as to recover not only tetracycline but the highest amount of their potential transformation products, which can cover a wide range of different physicochemical properties. The preliminary results indicate the generation of oxytetracycline, the (6S, 12aS)-3, 6, 10, 12, 12a-pentahydroxy-6-methyl-1, 4, 11-trioxo-1, 4, 4a, 5, 5a, 6, 11, 12a - octahydrotetracene-2-carboxamide and anhydrotetracycline.

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Cytostatics in the environment: analysis and occurrence.

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Cytostatics are a major class of chemotherapy drugs used extensively in the fight against cancer. The increasing consumption of cytostatic compounds raises concerns about their presence and effects in the aqueous environment. Only recently with developments in chromatography and mass spectrometry has their determination in environmental concentrations (sub ng/L) become possible. Our lecture will present the state of the art in analysis and occurrence of 5-fluorouracil, a common cytostatic, in the aqueous environment with an emphasis on an analytical method developed in our laboratory that gives the lowest LOQ for waste and surface waters: 1.6 ng/L and 0.54 ng/L, respectively. The method was used to analyse samples of hospital, wastewater treatment plant influent and effluent and surface waters. 5-fluorouracil was quantified in four out of the twelve samples of oncological ward wastewaters and municipal wastewater treatment plant influents in concentrations from 4.7 to 92 ng/L.

The reliability and comparability of analytical data is often limited, because analytical methods for emerging pollutants are often not fully validated, harmonised or suitable for all relevant matrices. Within the EU FP7 CytoThreat we organised an interlaboratory study on the determination of the most common cytostatics including 5-fluorouracil. The main goals were to evaluate the existing methods, as well as the influence of the analytical method and sample matrices on the results. The current results for this interlaboratory exercise will be presented at the workshop.

Multi-analyte determination of 26 cytostatics and metabolites by liquid chromatography-electrospray-tandem mass spectrometry: optimization, analytical performance, and study of the stability and optimum storage conditions for their determination in wastewater

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Nowadays, the demand of cytostatics in developed countries has increased. Many of them have been categorized as carcinogenic, mutagenic and teratogenic compounds even at low concentrations [1]. These compounds and their human metabolites are usually directly discharged into the sewage system without any specific control after being administered in the hospitals or by out-patients. Their levels in the environment, though very little investigated, appear relatively low (ng/L to µg/L) [2] as compared to those of other groups of pharmaceuticals; however, due to their highly potent mechanism of action, this specific group of drugs is conceived to be harmful to aquatic organisms and even human health.

The simultaneous multi-analyte determination of cytostatics is rather challenging due to their wide variety of physical-chemical properties and the instability of some of them in aqueous solution. This work describes the development of an analytical method based on liquid chromatography-electrospray-tandem mass spectrometry (LC-ESI-MS/MS) for the determination of up to 26 cytostatics, and investigates the stability of the target compounds in aqueous solution and in wastewater for up to three months under different conditions of pH and temperature. To the authors' knowledge, apart from some simulating processes using OECD mediums for cyclophosphamide, 5-fluorouracil, cisplatin, gemcitabine, cytarabine and methotrexate [3-5], the long-term stability of cytostatics in sewage or natural waters has not been investigated. The results obtained point out storage at -20 ºC immediately after collection as the best option. On the other hand, acidification of the samples improved the stability of some compounds.

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Identification of ozonation and chlorination by-products of ciprofloxacin by analysis by LC/HR-MS

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Pharmaceutically active substances can be excreted after human consumption in the different environmental matrices. Indeed significant amounts of the original or metabolized substance enter in the environment mainly via wastewater treatment plants.
So these pharmaceutical compounds can undergo transformations during sewage water treatment or drinking water treatment to generate transformation products.
This work is a part of the European FP7 Pharmas project (EU grant agreement Nr. 265346) and focus on two groups of antibiotics compounds and anticancer drugs and their fate during different treatments in terms of by-products and toxicity.
Five compounds are investigated: four anticancer drugs and one antibiotic, ciprofloxacin.
The elucidation of stable transformation products formed during different water treatment process was investigated for the 5 compounds.
The aim of our work is to elucidate stable transformation products of ciprofloxacin (antibiotic compound).
The applied methodology is the following:

- Application of the drinking water treatment process in laboratory scales
- Determination of ciprofloxacin removal in treated samples
- Identification of the transformation products formed during the treatment

Different treatments are studied: chlorination, ozonation and the combination ozonation + chlorination.
For treatment process, tests are performed with pure water and the spiking concentration is 1 mg/L per each parent compound. For operating parameters, the concentrations of chlorine and ozone have been chosen in order to simulate realistic industrial conditions in terms of doses and reaction time.
Treatments using these techniques may even lead to the formation of transformation products that are may be potentially more toxic than the parent compound. This is why toxicity tests have been also included in this global work.

The technique of liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS) is implemented to elucidate the structure of the stable transformation products formed. Moreover, targeted analysis is carried out for the ciprofloxacin compound in order to determine its removal for each treatment. Before LC-HRMS analysis, samples are extracted by two different techniques: liquid/liquid extraction and solid phase extraction. These two techniques used different solvents and they are based under different principles so the aim of the combination of the two extractions is to be the less specific possible to recover as much as possible the transformation products.

The purpose of this work is to present the results obtained for ciprofloxacin. The presentation will be divided in two parts. Firstly, the methodology applied will be detailed and secondly, first results of transformation products will be presented.

Identifications of phototransformation products of antiviral zanamivir with HILIC-LTQ-Orbitrap-MS in aqueous matrices

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During the influenza pandemic in 2009, the use of the antiviral zanamivir rose as Tamiflu (oseltamivir)-resistant H1N1 virus was recorded during the 2008–09 flu season in Japan. A considerable fraction of this drug was believed to be used for human treatment, and thus this metabolically stable compound ended up in untreated sewage. Although the reported concentrations of zanamivir in surface waters (up to 20 ng/L) were lower as compared to those pharmaceuticals frequently monitored in the aquatic environment, awareness should be kept on the selection of resistant strains of virus in the aquatic fauna. In this work we studied the susceptibility of zanamivir to photodegradation which is considered a key process governing the whereabouts of organic micro-pollutants in surface waters. Irradiation experiments were carried out under simulated solar irradiation using a Suntest apparatus as well as by exposure to natural sunlight during autumn of 2009.

The chromatographic analysis of zanamivir was initially attempted employing an RP-C18 column. Due to the high polarity of the analyte, however, no retention was achieved (tr of 0.54 min) even at a methanol percentage in the mobile phase of as low as 2 % at starting conditions. Furthermore, such conditions were far from optimal in view of minimizing potential interferences from matrix components. Therefore, the alternative suggested in the literature [1] was to use a HILIC column as this was expected to accommodate not only the parent compound but also any photoproducts being potentially more polar than zanamivir.

For the identification of transformation products assessment, HILIC was coupled to high-resolution LTQ-Orbitrap-MS. Low resolution tandem MS on a triple quadrupole MS was employed for studying the photolysis kinetics in different synthetic and natural matrices. Upon exposure of an aqueous solution (20 μg/L) to light emitted by a xenon lamp, zanamivir degraded with a half-life of 1.6 h, while the degradation was slower in artificial freshwater. Under the influence of natural sunlight the photodegradation of zanamivir spiked into pure water was negligible. On the other hand, in surface water about 40 % of the initial concentration of the antiviral disappeared within 30 days. Using HILIC-LTQ-Orbitrap-MS, three transformation products of zanamivir, spiked at 40 mg/L, were tentatively identified showing [M+H]+ ions at m/z 112 (termed as TP111), m/z 323 (TP322), and m/z 333 (TP332), respectively. However, only the formation of the lightest transformation product among the three was observed in photodegradation experiments performed at a zanamivir concentration of 20 μg/L. Under artificial irradiation, this photoproduct proved to be relatively persistent reaching a maximum concentration between 30 and 60 h. In summary, the findings suggest that the photodegradation of zanamivir in surface waters proceeds with slow kinetics.

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Degradation and transformation of 5-fluorouracil and capecitabine.

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5-Fluorouracil (5-FU) is a fluorinated pyrimidine analogue important in the treatment of cancer. Capecitabine (CAP) is its prodrug, a fluoropyrimidine carbamate, which is rapidly metabolised to the active substance 5-fluorouracil in the body. Yet, not all the administered drug is metabolised. The remainder, a mixture of parent compounds and metabolites, are excreted from the body and typically enter the sewerage system eventually reaching surface waters. Little, if anything, is known about their eventual fate and environmental transformation.

This work is the first to study the environmental transformation of 5-FU and CAP. Their removal and transformation was simulated using a series of biodegradation and photodegradation experiments, where 5-FU proved more degradable in comparison to CAP. Transformation of 5-FU and CAP was studied by using ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC–QqTOF). Overall, six transformation products for 5-FU and ten for CAP are proposed; 13 of these are to our knowledge published for the first time.

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