Chemosphere 190 (2018) 417–430

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

A case study to identify priority cytostatic contaminants in hospital effluents

A. Olalla [a], N. Negreira [b, c], M. López de Alda [b], D. Barceló [b, d], Y. Valcárcel [a, e, *]

[a] Research Group in Environmental Toxicology and Risk Assessment (TAyER), Rey Juan Carlos University, Avda Tulipán. s/n, 28933 Móstoles, Madrid, Spain
[b] Water and Soil Quality Research Group, Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Jordi Girona 18-26, 08034 Barcelona, Spain
[c] International Iberian Nanotechnology Laboratory (INL), Avda, Mestre José Veiga s/n, 4715 Braga, Portugal
[d] Catalan Institute for Water Research (ICRA), H2O Building, Scientific and Technological Park of the University of Girona, Emili Grahit 101, 17003 Girona, Spain
[e] Department of Medicine and Surgery, Psychology, Preventive Medicine and Public Health, Immunology and Medical Microbiology, Faculty of Health Sciences, Rey Juan Carlos University, Avda. Atenas, s/n, 28922 Alcorcón, Madrid, Spain

HIGHLIGHTS

- Concentrations of seven of the 17 cytostatic agents analysed, ranging from 25 to 4761 ng/L, were detected.
- The highest concentrations corresponded to ifosfamide, methotrexate and cyclophosphamide.
- Ifosfamide, imatinib and irinotecan presented the highest HQ values and therefore present the highest environmental risk.
- Three substances, namely ifosfamide, irinotecan and imatinib, which should be the focus of environmental monitoring, were identified.

ARTICLE INFO

Article history:
Received 26 April 2017
Received in revised form
20 September 2017
Accepted 26 September 2017
Available online 28 September 2017

Handling Editor: Klaus Kümmerer

Keywords:
Cytostatic agents
Priority contaminants
Hospital effluents
Environmental risk
Environmental hazard

ABSTRACT

This study analyses the presence of 17 cytostatic agents from seven different groups, based on their different mechanisms of action, in the effluent from a medium-sized hospital located in eastern Spain. Analysis of the compounds found in the effluents studied involved solidphase extraction (SPE) coupled on-line to a high performance liquid chromatograph tandem mass spectrometer (HPLC-MS/MS). The environmental risk of the compounds studied was then assessed by calculating the hazard quotient (HQ), combining the measured environmental concentrations (MECs) with dose-response data based on the predicted no effect concentrations (PNECs). In addition, the environmental hazard associated was evaluated in accordance with their intrinsic characteristics by calculating the PBT (Persistence Bioaccumulation Toxicity) index. The results of this study showed the presence of seven of the 17 compounds analysed in a range of between 25 and 4761 ng/L. The highest concentrations corresponded to ifosfamide (58–4761 ng/L), methotrexate (394–4756 ng/L) and cyclophosphamide (46–3000 ng/L).

Assessment of the environmental hazard showed that the three hormonal agents (tamoxifen and its metabolites endoxifen and hydroxytamoxifen) exhibited a maximum PBT value of 9 due to their inherent harm to the environment resulting from their characteristics of persistence, bioaccumulation and toxicity.

A combined evaluation of the risk and environmental hazard showed that three of the 17 compounds studied, namely, ifosfamide, imatinib and irinotecan, all of which exhibited HQ values higher than 10 and PBT indices of 6, indicative of a particularly high potential to harm the environment, deserve special attention.

1. Introduction

Drugs have been discharged into the environment without restrictions for many years as wastewater treatment plants (WWTPs)

* Corresponding author. Research Group in Environmental Toxicology and Risk Assessment (TAyER), Rey Juan Carlos University, Avda Tulipán. s/n, 28933 Móstoles, Madrid, Spain.
E-mail addresses: adrianolalla@gmail.com (A. Olalla), Yolanda.valcarcel@urjc.es (Y. Valcárcel).

https://doi.org/10.1016/j.chemosphere.2017.09.129
0045-6535/

Abbreviations

ACS	American Cancer Society
AF	Assessment Factor
ATC	Anatomic Therapeutic Classification
BCF	Bioconcentration Factor
CAP	Capecitabine
ChV	Chronic Values
CP	Cyclophosphamide
CTM	Carcinogenicity, Teratogenicity, Mutagenicity
ECOSAR	Ecological Structure-Activity Relationships
EPA	Environmental Protection Agency
EPSAR	Public Wastewater Sanitation Entity
EU	European Union
HE	Hospital Effluent
HPLC-MS/MS	High Performance Liquid Chromatography coupled to tandem Mass Spectrometry
HQ	Hazard Quotient
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IF	Ifosfamide
IMA	Imatinib
IRI	Irinotecan
LC(E)50	Median Lethal (Effective) Concentration
LDet	Limit of Determination
LOD	Limit of Detection
MEC	Measured Environmental Concentration
MET	Methotrexate
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Co-operation and Development
OH-MET	Hydroxymethotrexate
OH-PAC	Hydroxypaclitaxel
OH-TAM	Hydroxytamoxifen
OH-D-TAM	Endoxifen
PBT	Persistence Bioaccumulation Toxicity
PNEC	Predicted No Effect Concentration
QSAR	Quantitative Structure-Activity Relationship
SEOM	Spanish Society of Medical Oncology
SMILES	Simplified Molecular Input Line Entry Specification
SPE	Solid Phase Extraction
SW	Surface Water
TU	Toxic Unit
UV	Ultraviolet
WHO	World Health Organization
WWTP	Wastewater Treatment Plant

are not specifically designed to remove such substances (Bound and Voulvoulis, 2005). It has been demonstrated that advanced secondary and tertiary treatments in such plants are poorly effective at removing these types of compounds and their metabolites excreted by the human body (Verlicchi et al., 2012), thus meaning that such treatment plants must be upgraded to include quaternary specialities such as ozonisation or ultraviolet system.

Given the above, these pharmacologically active substances are constantly entering the water cycle. Moreover, consumption of these drugs worldwide is increasing as both the life expectancy and standard of living of the population increase (Kümmerer, 2010). As such, measures must be taken and solutions adopted given the expected increase in the concentration of these pharmacological compounds in natural waters.

Although many members of the Organization for Economic Cooperation and Development (OECD) have restricted and controlled the use of numerous drugs over the past few years, the consumption of some categories of drugs continues to increase given their increasing use to treat chronic diseases and those typically found in the elderly (OECD, 2013). Moreover, the fact that analytical techniques have improved markedly over the past few years, to such an extent that these compounds can now be detected at ng and sub-ng/L levels, has increased interest in them and the efforts dedicated to investigating their presence and potential impact on the aquatic environment (Fatta-Kassinos et al., 2011) (Verlicchi et al., 2012).

It is suspected that drugs used to treat cancer present a specific risk for aquatic species, and possibly also for human health, once they have passed through treatment plants and entered the water cycle (Kümmerer, 2001). Taking into account their different mechanisms of action, it is possible that, given the design of these molecules, they may interact directly or indirectly with DNA, thus damaging it or inhibiting its synthesis, as well as affecting mitosis or cell proliferation (Toolaram et al., 2014). Consequently, these mechanisms of action may non-specifically inhibit other cells, thereby representing a hazard for organisms.

A total of 215,534 new cancer cases were reported in Spain in 2012. Taking into account the demographic evolution predicted by the United Nations, 246,713 new cases of cancer are forecast to be diagnosed in Spain by 2020 (SEOM, 2016).

Considering the cases reported in Spain and neighbouring countries, cancer is the leading cause of mortality worldwide, with approximately 14 million new cases in 2012 (WHO, 2012). Moreover, current forecasts predict that the number of new cases diagnosed will increase by 70% in the next few decades.

Cytostatic drugs are used in chemotherapy to treat oncological patients. Cancer is a disease resulting from uncontrolled cell growth, and these drugs (which represent one of the three main anti-cancer treatments) are intended to prevent the growth and proliferation of cancer cells.

Cytostatic agents are classified as antineoplastic agents and immunomodulators (Class L) in the World Health Organization (WHO) Anatomic Therapeutic Classification (ATC) (Table 1).

Since these drugs are designed to damage DNA, inhibit its synthesis and disrupt cell replication, they bring together all the characteristics necessary to have a negative impact on the environment (Kosjek and Heath, 2011).

Given that the use of these drugs in hospitals has increased as a result of the marked increase in the number of cancer patients, hospitals are one of the main sources via which these substances reach the environment. Many of these agents are not fully metabolised upon administration and are therefore excreted by patients into hospital waste flows, from where they reach the sewers and, finally, rivers (Turci et al., 2003).

Table 1
Anatomical Therapeutic Classification of cytostatic drugs.

Antineoplastic and Immunomodulating Agents (Class L)	
Class L01 - Cytotoxic drugs	Class L02 - Endocrine therapy drugs
Class L01A - Alkylating agents	
Class L01B - Antimetabolites	
Class L01C - Plant alkaloids	
Class L01D - Cytotoxic antibiotics	
Class L01X - Other antineoplastic agents	