Environment International 86 (2016) 107–118

Contents lists available at ScienceDirect

Environment International

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

Drugs of abuse, cytostatic drugs and iodinated contrast media in tap water from the Madrid region (central Spain):A case study to analyse their occurrence and human health risk characterization

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ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form 15 October 2015
Accepted 2 November 2015
Available online xxxx

Keywords:
Pharmaceuticals
Illicit drugs
Anti-cancer drugs
Drinking water
Human health risk characterization

ABSTRACT

This work analyses the presence of forty-eight emerging pollutants, including twenty-five drugs of abuse and metabolites, seventeen cytostatic drugs and six iodinated contrast media, in tap water from the Madrid Region. Analysis of the target compounds in the tap water was performed by means of (on-line or off-line) solid-phase extraction followed by analysis by liquid chromatography–tandem mass spectrometry. A preliminary human health risk characterization was undertaken for each individual compound and for different groups of compounds with a common mechanism of action found in tap water.

The results of the study showed the presence of eight out of the twenty-five drugs of abuse and metabolites analysed, namely, the cocainics cocaine and benzoylecgonine, the amphetamine-type stimulants ephedrine, 3,4-methylenedioxymethamphetamine and methamphetamine, the opioid methadone and its metabolite 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine and, finally caffeine at concentrations ranging from 0.11 to 502 ng L^{-1}. Four out of the six analysed iodinated contrast media, namely, diatrizoate, iohexol, iomeprol and iopromide, were detected in at least one sample, with concentration values varying between 0.4 and 5 ng L^{-1}. Cytostatic compounds were not detected in any sample. Caffeine was the substance showing the highest concentrations, up to 502 ng L^{-1}, mainly in the drinking water sampling point located in Madrid city. Among the other drugs of abuse, the most abundant compounds were cocaine and benzoylecgonine, detected at concentrations ranging from 0.11 to 86 ng L^{-1} and from 0.11 to 53 ng L^{-1}, respectively. Regarding iodinated contrast media, iohexol was the most ubiquitous and abundant compound, with a frequency of detection of 100% and concentrations from 0.5 to 5.0 ng L^{-1} in basically the same range in all sampling points.

Taking into account the results and types of treatment applied, ozonisation plus granular activated carbon filtration appears to be efficient in the removal of cocaine and benzoylecgonine. For the amphetamine-type

Abbreviations: 6ACM, 6-acetylmorphine; ADI, acceptable daily intake; ALP, alprazolam; AM, amphetamine; ATC, Anatomical Therapeutic Classification; ATS, amphetamine-type stimulant; BE, benzoylecgonine; BQ, benchmark quotient; BW, body weight; CAF, caffeine; CBD, cannabidiol; CBN, cannabinol; CE, cocaethylene; CF, coagulation-flocculation; CO, cocaine; CP, cyclophosphamide; D, decantation; DAs, drugs of abuse; DF, disinfection; DIA, diazepam; DIAT, diatrizoate; DWEL, drinking water equivalent level; DWSP, drinking water sampling point; DWTP, drinking water treatment plant; ECHA, European Chemicals Agency; EDADES, Spanish household survey on alcohol and drugs; EDDP, 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine; EFSA, European Food Safety Authority; EP, emerging pollutant; EPH, ephedrine; GAC, granular activated carbon; GACF, granular activated carbon filtration; HER, heroin; IARC, International Agency for Research on Cancer; ICM, iodinated contrast media; IDX, iodixanol; INE, Spanish Statistics Institute; IngR, drinking water ingestion rate; IOH, iohexol; IOM, iomeprol; IOP, iopromide; IPM, iopamidol; KET, ketamine; LC, liquid chromatography; LO(A)EL, lowest observed (adverse) effect level; LOD, limit of detection; LOQ, limit of quantification; LOR, lorazepam; LSD, lysergic acid diethylamide; MA, methamphetamine; MEPH, mephedrone; MDMA, 3,4-methylenedioxymethamphetamine; MEC, measured environmental concentration; METH, methadone; MS/MS, tandem mass spectrometry; MS, mass spectrometry; MOR, morphine; MR, Madrid Region; MSSSI, Spanish Ministry of Health, Social Services and Equality; n.a., not available; NO(A)EL, no observed (adverse) effect level; O-OH-LSD, 2-oxo-3-hydroxy-LSD; OH-THC, 11-hydroxy-THC; PET, polyethylene terephthalate; OZ, ozonisation; PCL, pre-chlorination; pGLV, provisional guideline value; POX, pre-oxidation; RfD, reference dose; RO, reverse osmosis; SF, sand filtration; SPE, solid phase extraction; SRM, selected reaction monitoring transition; TDI, tolerable daily intake; THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; TP, transformation product; UF, uncertainty factor; UFT, ultrafiltration; UNODC, United Nations Office on Drugs and Crime; US EPA, United States Environmental Protection Agency; WHO, World Health Organization; WWTP, wastewater treatment plant.

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http://dx.doi.org/10.1016/j.envint.2015.11.001

stimulants, opioids and caffeine, ozonisation plus granular activated carbon filtration and ultrafiltration plus reverse osmosis showed higher removal efficiency than sand filtration.
The human health risk characterization performed indicates that the lifetime consumption of the tap waters analysed has associated a negligible human health concern.

1. Introduction

In the last twenty years, there has been an increasing concern about the occurrence and adverse effects of emerging pollutants (EPs), defined as new chemicals without regulatory status and whose impact on environment and human health is poorly understood (Deblonde et al., 2011). This category of pollutants comprises a wide range of different substances with varying chemical structures and applications (e.g. industrial, urban, domestic) and, among them, pharmaceuticals, including both licit and illicit or abused substances, are of particular concern because of their large production and use and designed biological activity.

Drugs of abuse (DAs) and some of their metabolites/transformation products (TPs) have been detected in the water cycle relatively recently (Pal et al., 2013), thanks to the development of advanced analytical methods for their determination in the different water matrices (González-Mariño et al., 2010; Postigo et al., 2008) and as a consequence of their widespread consumption (UNODC, 2014) and irregular elimination in water treatment plants (Boleda et al., 2011a; Postigo et al., 2011a). Caffeine, apart from being one of the most widely consumed stimulant drugs throughout the world may be considered in addition to an abused substance (Gilliland and Bullock, 1983-1984) a marker of anthropogenic contamination due to its extended use, chemical stability, widespread detection in the environment, and relationship with other contaminants associated to human activities found in waters (Buerge et al., 2003; Ferreira and da Cunha, 2005; Valcárcel et al., 2011).

Within the class of licit pharmaceuticals, iodinated contrast media (ICM) and cytostatic compounds are among the least investigated in the water cycle. Cytostatic drugs are used mainly in hospitals for the treatments of oncological patients. Due to their mechanism of action many of these pharmaceuticals pose cytotoxic, mutagenic, carcinogenic, embryotoxic and/or teratogenic effects (Negreira et al., 2013). The use of pharmaceuticals for cancer therapy has considerably increased in the last decade (Mahnik et al., 2007; Nussbaumer et al., 2011) and this tendency is only expected to continue. According to the last World Cancer Report of the International Agency for Research on Cancer (IARC) this illness is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012, and annual cancer cases are expected to rise from 14 million in 2012 to 22 million within the next two decades (WHO, 2014). Studies investigating the occurrence of anticancer drugs in the environment are recent and scant (Besse et al., 2012; Kosjek and Heath, 2011; Negreira et al., 2013; Santos et al., 2010; Verlicchi et al., 2012), as are the methods developed for their determination in water and the information on their behaviour, removal and fate in the water cycle (Zhang et al., 2013; Negreira et al., 2014).

ICM are the pharmaceuticals most frequently used in hospitals (Hirsch et al., 2000) for radiological and medical diagnostic purposes. Their high use (Pérez and Barceló, 2007), lack of human metabolism (Weissbrodt et al., 2009), and variable removal in conventional (Clara et al., 2005) and advanced (Boleda et al., 2011a) wastewater treatments has led to their finding in the water cycle, with the aggravating circumstance that hospitals and radiological clinics effluents are usually discharged into the public wastewater system without previous treatment (Santos et al., 2010, 2013; Mendoza et al., 2015).

The presence of this kind of pollutants and their metabolites/TPs in wastewater, surface water and groundwater implies a potential for indirect human exposure to them via drinking water supplies (Webb et al., 2003). Fig. 1 shows how these pollutants can enter the water cycle and reach tap water. In comparison with other types of water, few studies have investigated the presence of DAs and pharmaceuticals in drinking water (Benotti et al., 2009; Boleda et al., 2009, 2011a, 2011b, 2013; Esteban et al., 2012, 2014; Huerta-Fontela et al., 2008, 2011; Jones et al., 2005; Kosjek and Heath, 2011; Kuster et al., 2008; Leung et al., 2013; Loos et al., 2007; Mendoza et al., 2014; Mompelat et al., 2009, 2011; Pérez and Barceló, 2007; Rahman et al., 2009; Rodil et al., 2012; Santos et al., 2010; Valcárcel et al., 2011, 2012, 2013). The report of their presence in this matrix and the absence of specific drinking water guideline values to regulate it have raised public concern. Furthermore, according to the critical review recently performed by Villanueva and col. on the human exposure and health consequences of chemicals in drinking water (Villanueva et al., 2014) there is a particular knowledge gap in the assessment of the human exposure via drinking water to a wide range of EPs and of the associated risks that requires investigation (Villanueva et al., 2014). In the last decade, a number of works have addressed these issues for DAs and pharmaceuticals and have proposed different approaches for their evaluation (Bruce et al., 2010; Leung et al., 2013; Mendoza et al., 2014; Snyder et al., 2010; Van der Aa et al., 2011; Wen et al., 2014), however, only a few of them have addressed mixture toxicity (De Jongh et al., 2012; Houtman et al., 2014; Kumar et al., 2010; Watts et al., 2007).

The Madrid Region (MR), with an estimated population of 6,495,551 inhabitants and a population density of 809 inhabitants per km^2, is the most densely populated region in Spain (INEbase, 2013). The average consumption of tap water in private residences in the MR (141 L $person^{-1}$ day^{-1}) is similar to the average in Spain (142 L $person^{-1}$ day^{-1}) although it is the third region in total volume consumption (13.8%) (INE, 2013). Tap water in this region originates from surface water coming from both reservoirs and rivers being treated afterwards in drinking water treatment plants (DWTPs). Although according to the 2011 report of the Spanish Ministry of Health, Social Services and Equality (MSSSI) the quality of the Spanish drinking water was suitable in 99.3% of the cases (MSSSI, 2011), it needs to be taken into account that in this kind of assessments the evaluation of the occurrence of EPs like those investigated in the present study is not mandatory and hence not considered.

In this context, the main objectives of the present study were: (i) to monitor the occurrence during 1 week of 48 EPs, including 25 DAs and metabolites, 6 ICM and 17 cytostatic drugs, in tap water from the three main supply areas in the MR, (ii) to analyse the differences in the obtained results in respect to the type of water treatments applied in each case, and (iii) to preliminary characterize the human risk associated to the exposure to the detected substances and their mixtures.

2. Materials and methods

2.1. Description of the sampling site

The MR is situated in Central Spain. Its area (1.6% of the Spanish territory) is the most densely populated region in Spain. Its capital, Madrid, with 3,207,247 inhabitants, holds 49% of the total MR population, and the municipalities investigated in the present study, namely, Alcorcon, Aranjuez and Titulcia possess 169,773, 57,728 and 1237 inhabitants, respectively (INEbase, 2013).

Grab tap water samples were taken in one sampling campaign carried out the second week of November 2013. One sample per day during