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Understanding the magnitude of emergent contaminant releases through target screening and metabolite identification using high resolution mass spectrometry: Illicit drugs in raw sewage influents

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HIGHLIGHTS

- A total of 54 phase I and II metabolites of illicits were reported.
- Data dependent scan and targeted MS^2 were explored for confirmation of metabolites.
- %mol fraction of each identified metabolite was reported.

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ABSTRACT

A QExactive Orbitrap was used for the identification of phase I and II transformation products (TPs) of illicit drugs in raw sewage influents. Two operating modes (targeted MS^2 and Data-dependent screening) were used for data acquisition. Even though, data-dependent scan is a faster route towards the potential identification of metabolites, it suffered from its limitation to provide enough data points across the chromatographic peak during the MS^2 cycle in contrast to targeted MS^2. Therefore, the later technique was implemented as the method of choice in this study for the positive confirmation and quantitation of TPs ($n = 54$). The vast majority of the identified TPs were products of phase I transformation reactions, with the latter being more prevalent in the nature. Estimated mole fractions showed that for a large number of the analytes, TPs must also be monitored in order to fully understand their environmental fate and calculate potential consumption.

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1. Introduction

The prevalence of illicit drug consumption continues to be a growing problem worldwide. In US alone, it was estimated that 23.9 million Americans aged 12 or older used illicit drug in 2012 [1]. These figures do not even consider the abuse of common prescription drugs such as Adderall (amphetamine) and Oxycontin (oxycodone) [2–4]. Upon consumption, drugs of abuse (DOA; illicits and prescription) are subjected to phase I and II metabolic transformations in the body. Phase I reactions involve hydrolysis, reduction, and oxidation, making their products slightly more hydrophilic than the parent by exposing or introducing functional groups such as –OH, $-NH_2$, –SH, or –COOH. In addition, Phase II reactions include glucuronidation, sulfation, acetylation, methylation, glutathione conjugation, and conjugation with amino acids such as glycine, taurine, and glutamic acid [5,6], also increasing the polarity of their transformation products (TPs) [7]. A combination of phase I and phase II TPs plus their unchanged parents are excreted via urine and/or faeces. Multiple studies have demonstrated that once these excretion products reach wastewater treatment plants, not all of the compounds can be efficiently removed prior to the release of effluent waters into aquatic environments [8–11]. Even treatment plants equipped with what could be classified as advanced treatment are not designed to eliminate these compounds from their effluents. Emission of these compounds will likely continue until new materials and or technologies are developed for their removal. Occurrence of DOAs in sewage influents, effluents, as well as surface waters, have previously been reported with concentrations reaching up to 27,500 ng/L [12]. Moreover, analysis of raw sewage water from small settings such as a college campus can provide further information on metabolic transformation products since the residence time of these compounds in the

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actual sewage is minimal compared to that of influent waters arriving at WWTPs where additional TPs can be produced by microbial activity during transit. For instance, amphetamine concentrations of 2100 ng/L were reported in a college campus in Oregon, when comparing this value to those reported by Chiaia from influent sewage waters throughout the US (550 ng/L), a loss of the parent compound is noted confirming the possibility of external transformations [2]. External transformations include photodegradation, hydrolysis, chemical oxidation and biodegradation, and could also be observed in aquatic environments, increasing the possibility of finding new metabolites that were not previously taken into account.

Assessment on the occurrence of illicit drugs have been for the most part monitored using the unchanged form of the drug (parent), and in some cases by the evaluation of very few well known metabolites [10,13–17]. Furthermore, it is sometimes critical to monitor metabolites since many compounds are excreted as glucuronide or sulfate conjugates and are likely to be transformed back into the parent molecule from adducts during treatment process [15,18]. As an example, deconjugation of one of the phase II metabolites of morphine and heroin (morphine-3β-D-glucuronide) is converted back into the parent molecule (morphine) once it reaches aquatic environments [19,20]. As in the case with antibiotics, lack of availability of metabolite standards in the market, diminishes the ability for identification of metabolites and other transformation products [21]. In any way, absence of the parent drug does not necessarily indicate lack of consumption, efficiency of treatment plants, or analytical issues with the method of detection; it could very well mean that there is simply not enough information on metabolic transformations to confirm their presence.

Robust and sensitive analytical tools are required to identify and confirm the low abundant metabolites (parts per trillion level) in the complex matrices. To date, high resolution mass spectrometric instruments such as the quadrupole-time-of-flight (qTOF), Fourier transform-ion cyclotron resonance (FT-ICR), and the Orbitrap have become the ideal tools for the identification of metabolites and transformation products, thanks to their high resolving power (30,000–1,000,000), high mass accuracy (<5 ppm), linear dynamic range, and sensitivity [5,22–24]. The Orbitrap is, however, gaining popularity for the identification of metabolites due to its sensitivity, large dynamic range and its ability to use an external calibration as opposed to an internal calibration to maintain high accuracy (as in the qTOF) [23,25,26].

In the recent years there have been some reports in the identification of new TPs for cocaine and codeine utilizing high resolution instruments as the ones mention above [27,28]. Bijlsma's group focused on the degradation products of cocaine and its major metabolite (benzoylecgonine) resulting from in lab controlled degradation experiments (e.g. chlorination, hydrolysis, and photodegradation. Four newly identified TPs were reported in this study, three of them were isomers. However, target screening of these TPs in influent, effluent, and surface waters was carried out using a TSQ (QqQ) mass spectrometer in SRM. The downside of this approach is that it increases the possibility for neglecting potential TPs that can arise from matrix interactions. In addition, a similar screening method to the one reported in this manuscript have been perform in the area of pesticides, validating the importance of combined target analysis and target screening for the efficient identification and monitoring of TPs [29].

Data acquisition is an important aspect in the process of TP identification when using an Orbitrap, since intensity threshold parameters and limited data points across the chromatographic peak can potentially omit useful data or, on the contrary, acquire unreliable data. Therefore, the objective of the present study is a threefold: (1) to develop and compare two workflows based on two different types of acquisition modes (targeted-MS^2 and data-dependent) to identify the most complete and reliable manner of data collection; (2) to implement these workflows in the identification of illicit drug metabolic contaminants of emerging concern; and (3) to further determine their abundances relative to their parent compounds from %mol fraction determinations, and their prevalence as a way to demonstrate the importance of their assessment.

2. Experimental

2.1. Reagents and chemicals

Illicit drug and metabolite standards as well as some of their deuterated analogues used in the analytical method cocaine (CO, cocaine-d3), benzoylecgonine (BE, benzoylecgonine-d3), cocaethylene (CE, cocaine-d3), codeine (COD, codeine-d6), morphine (MO, morphine-d6), 6-acetylmorphine (6-AMO, morphine-d6), oxycodone (OXY, oxycodone-d6), methadone (ME, methadone-d9), EDDP (methadone-d9), heroin (HE, morphine-d6), LSD (LSD-d3), Δ-9-THC (THC, Δ-9-THC-d3), 11-nor-9-carboxy-Δ-9-THC (THC-COOH, 11-nor-9-carboxy-Δ-9-THC-d3), amphetamine (AM, amphetamine-d5), MDA (MDA-D5), MDEA (MDEA-D6), MDMA (MDMA-D5), and, methamphetamine (MA, Methamphetamine-d14). However, 6-AMO and HE were never detected, nor any possible TPs, therefore they were left out of the rest of the study. Standards and deuterated analogues were purchased from Cerilliant (Round Rock, TX, USA). Standard stock solutions containing target analytes or deuterated compounds were prepared at a concentration of 20 μg/L in methanol and stored in the dark at −20 °C. Optima LC/MS grade methanol, water, and acetonitrile were purchased from Fisher Scientific (Fair Lawn, NJ, USA) and used for standard preparation and HPLC mobile phases. Optima LC/MS grade formic acid was purchased from Fisher Scientific (Fair Lawn, NJ, USA) and used to prepare 0.1% solutions for modifier mobile phase. 1.0 and 0.45 μm PreSep Prefilter, glass filters were purchased from Fisher Scientific (Fair Lawn, NJ, USA).

2.2. Sample collection and preparation

A total of 12,200 mL grab influent raw sewage water samples were collected during the month of April 2013 from the main lift station at a college campus using an automated ISCO sampler. Samples were transported to the laboratory and were filtered using a 1.0 μm PreSep Prefilter glass filter followed by 0.45 μm PreSep Prefilter glass filter. Samples were stored in clear polyethylene terephthalate (PET) bottles in the dark at −20 °C until the time of analysis. Filtration of the sample is essential to remove most of the matrix components including bacteria. Therefore, very minimal or no biological activity, or photodegradation should be observed in the dark and at −20 °C [30,31]. On the day of analysis raw sewage water samples were allowed to thaw at room temperature and shaken for about 10 s. Samples were diluted ten times (10×) in deionized water (DI) water, and fortified with the appropriate internal standards (200 ng/L). A seven-point calibration curve (5 ng/L–500 ng/L) containing illicit standards and their deuterated analogues was prepared using DI water.

2.3. Pre-concentration and chromatographic separation of analytes

Pre-concentration of samples was achieved using an EQuan online solid phase extraction (SPE) system from Thermo Scientific (Waltham, MA, USA). The on-line EQuan SPE procedure has been explained in detail elsewhere [32,33]. In short, the pre-concentration and analytical separation of analytes were performed using a Thermo EQuan Max online-SPE system equipped

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