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A snapshot of illicit drug use in Sweden acquired through sewage water analysis

Marcus Östman *, Jerker Fick, Elin Näsström, Richard H. Lindberg

Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden

HIGHLIGHTS

- An online-SPE LC–MS/MS method for illicit drugs was developed.
- Incoming water from 33 sewage treatment plants was analyzed for illicit drugs.
- Regional drug consumption differences were highlighted by multivariate data analysis.
- The differences were supported by prescription statistics for pharmaceuticals.

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ABSTRACT

Analytical measurements of sewage water have been used many times to estimate the consumption of specific drugs in an area. This study measured a large number of illicit drugs and metabolites (>30) at a large number of sewage treatment plants (STPs) distributed across Sweden. Twenty-four illicit and prescription drugs, classified as narcotic substances in Sweden, and seven selected metabolites were included in the study. A 24 hour composite sample of incoming sewage water was collected from 33 different municipalities at various geographic locations across Sweden. Species were analyzed using an on-line solid-phase extraction–liquid chromatography electrospray tandem mass spectrometry method. The method proved to be rapid with minimum need for sample work up and was able to detect 13 compounds above their respective limits of quantification. The results for all compounds were presented as per capita loads. Multivariate data analysis was used to relate drug consumption to geographical location and/or population of cities. The results showed that geographical differences in drug consumption were apparent across the country. For the narcotic pharmaceuticals, the geographical differences suggested by the multivariate model were supported by prescription statistics.

1. Introduction

The monitoring of illicit drug use in a given community is an important tool for improving public health. Traditionally, this has been carried out by indirect methods, such as population surveys, medical records, and data on seizures (European Monitoring Centre for Drugs and Drug Addiction, 2002). Daughton (2001) suggested that it should be possible to back calculate the use of illicit drugs from levels measured in incoming sewage water. Zuccato et al. confirmed that this was feasible in 2005 and since then, several studies have been published (Baker and Kasprzyk-Hordern, 2013, 2011a; Bijlsma et al., 2012; Chiaia et al., 2008; de Voogt et al., 2012; Fontanals et al., 2013; Karolak et al., 2010; Lin et al., 2010; Postigo et al., 2011, 2008; Reid et al., 2011; Terzic et al., 2010; Thomas et al., 2012; van der Aa et al., 2013; van Nuijs et al., 2011a, 2011b, 2009a, 2009b; Zuccato et al., 2005). These types of measurements are a valuable complement to classic methods as they are generally faster and less labor intensive.

Back calculation from measured levels in sewage water to usage in a community is an approach that is still under development and several factors need further investigation. Castiglioni et al. (2013) have conducted an investigation of the whole process from sampling to back calculation to evaluate the uncertainty of all steps. Khan and Nicell (2012, 2011) have recently made in-depth studies of the mass balances of cocaine, heroin, ecstasy, methamphetamine, amphetamine and tetrahydrocannabinol (THC). For these illicit drugs, the excretion pattern for the major metabolites is known, which is an essential factor in back calculations. To make a good back calculation, it is crucial to know which metabolite to use and to what extent it is excreted from the body. Another important factor that may bias the results is the number of people served by each plant. Since this may differ dramatically, e.g., due to commuting, special events, or seasonal changes, a static approach has several disadvantages, as pointed out by Van Nuijs et al. (2011b). Alternative methods, e.g., using parameters such as the biological oxygen demand (BOD) and chemical oxygen demand (COD) to calculate the number

* Corresponding author. Tel.: +46 90 786 9320.
E-mail address: marcus.ostman@chem.umu.se (M. Östman).

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of people connected each day, have the advantage of reflecting relevant fluxes in the population. Unfortunately, it is impossible to differentiate the industrial load from the domestic load. Adsorption of drugs to particulate matter in sewage water may also influence the results. However, Baker and Kasprzyk-Hordern (2011a) have recently shown that many illicit drugs adsorb by less than 10% to particulate matter, with the exceptions of methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).

Monitoring studies can be labor-intensive and time-consuming, mostly due to the manual steps involved in the pre-treatment, e.g., filtration and solid phase extraction (SPE). This problem can be minimized by using semi-automated on-line SPE techniques. On-line methods are generally more rapid, precise and efficient than conventional techniques because they eliminate time-consuming evaporation and reconstitution steps and require minimal sample handling. On-line SPE is also more environmentally friendly since it requires less solvent, has a high sample throughput and utilizes comparatively small sample volumes. One major drawback of on-line SPE methods is that they generally have lower pre-concentration factors in comparison to off-line SPE of aqueous environmental samples, and therefore slightly higher method limits of quantification (LOQs). Nevertheless, on-line SPE has been used successfully in the analysis of both biological and environmental samples for various analytes (Fontanals et al., 2013, 2011; Khan et al., 2012; Lopez-Serna et al., 2010; Postigo et al., 2008; Segura et al., 2007). Several on-line methods have also been developed and used in studies of illicit drugs (Fontanals et al., 2013, 2011; Ghassabian et al., 2012; Postigo et al., 2008; Saussereau et al., 2012; and also reviewed by Vazques-Roig et al., 2013). However, most previous studies were not developed to study illicit drugs in incoming wastewater, and to the best of our knowledge, the studies of Postigo et al. (2008) and Fontanals et al. (2013) are the only ones to employ online methods for sewage water analysis of illicit drugs.

The use of illicit drugs often varies with location and has been investigated with sewage water analysis before (Thomas et al., 2012). We propose that a better way to detect patterns in the consumption of illicit drugs and prescription narcotic substances is to subject the data to multivariate data analysis, providing an easy way of obtaining an overview of illicit drug consumption.

The aims of this study were (a) to develop a method for measuring 24 illicit and prescription narcotic substances and seven of their metabolites in incoming sewage water using an efficient on-line SPE method, (b) to acquire a snapshot of the usage of illicit drugs in different municipalities/cities in Sweden, and (c) to investigate if drug use is dependent on the size of the city and/or its geographical location.

2. Materials and methods

2.1. Selection of illicit drugs

The selection of illicit drugs included in this study was based on a) information on the established illicit drugs in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2013b), b) previous findings from studies in sewage waters (Baker and Kasprzyk-Hordern, 2013, 2011a, 2011b; Bijlsma et al., 2012; Chiaia et al., 2008; de Voogt et al., 2012; Fontanals et al., 2013; Karolak et al., 2010; Lin et al., 2010; Postigo et al., 2011, 2008; Reid et al., 2011; Terzic et al., 2010; Thomas et al., 2012; van der Aa et al., 2013; van Nuijs et al., 2011a, 2011b, 2009a, 2009b), and c) plausible emerging illicit drugs (or metabolites thereof) mentioned in various open access web forums.

2.2. Chemicals and reagents

For all standards and eluents, Milli-Q (resistivity 18.2 MΩ cm^{-1}) water from a Millipore gradient ultrapure water system (Millipore, USA) was used. Methanol (Liqrosolve, Hypergrade) used in eluents were bought from Merck (Darmstadt, Germany) and formic acid (puriss. p.a.) was obtained from Fluka (Steinheim, Germany). Amphetamine, benzoylecgonine, cathinone HCl, 6-acetylmorphine, cocaine, heroin, ketamine HCl, n-methyl-1,3-benzodioxolylbutanamine (MBDB) HCl, 3,4-methylenedioxyamphetamine (MDA), methylenedioxyethylamphetamine (MDEA), 3,4-methylenedioxy-N-methylamphetamine (MDMA), methamphetamine, methylphenidate, midazolam, norketamine HCl, lysergic acid diethylamide (LSD), 2-oxo-3-hydroxy-LSD, oxycodone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) perchlorate, methadone, norbuprenorphine glucuronide, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH), 6-acetylmorphine-D6, amphetamine-D5, benzoylecgonine-D8, cocaine-D3, heroin-D9, MDA-D5, MDMA-D5, methadone-D9, methamphetamine-D5 and THC-COOH-D9 were bought from Cerilliant (Texas, USA) as 0.1 or 1 mg/mL standards in either methanol or acetonitrile. Alprazolam, buprenorphine HCl, codeine, fentanyl, flunitrazepam, morphine sulphate, oxazepam and zolpidem were purchased from Sigma Aldrich. Mephedrone was bought from the National Measurement Institute (Australia). Tramadol was bought from the Council of European Pharmacopoeia (Strasbourg) as 0.1 or 1 mg/mL standards in either methanol or acetonitrile. Codeine-D6, oxazepam-D5 and tramadol-C13-D3 were purchased from the Cambridge Isotope Laboratories (Andover, MA, USA). All substances were classified as >99% pure except for 2-oxo-3-hydroxy-LSD (>97.7%) and LSD (>98.9%). All substances were stored according to the supplier's instructions.

2.3. Sampling and pretreatment

Sewage treatment plants (STPs) were selected for sampling to achieve a wide geographical distribution across Sweden. In total, 33 plants were included, with all but two having more than 10,000 people connected to the STP (see Fig. 1). Samples, i.e., 24 hour flow proportional composite samples of incoming sewage water, were collected by the staff of each plant in January 2012. All samples were supposed to be collected on the same date – the 17th January 2012 (a Tuesday) – but some exceptions were made (see sampling dates listed in Table 1). Additional parameters measured in the wastewater are detailed in Table S14 of the Supplementary Information. Only one sample per STP was collected for practical reasons. Samples had to be collected during a weekday since it was difficult to obtain weekend samples from such a large number of STPs. Samples were collected in 250 mL high density polyethylene bottles (HDPE) and were sent frozen to the laboratory for analysis. Prior to injection on the analytical instrumentation, samples were thawed and subjected to syringe filtration (0.45 μm Filtropur S, Sarstedt, Nümbrecht, Germany), addition of internal standards (ISs) (to a final concentration of 500 ng L^{-1}) and acidification to pH 3 using formic acid (FA).

2.4. Analytical instrumentation

A Thermo TSQ Quantum Ultra (Thermo Fisher Scientific, San Jose, CA, USA) mass spectrometer was used. Samples were injected using a PAL HTC auto sampler (CTC Analytics AG, Zwingen, Switzerland) into a 1 mL stainless steel loop. The auto sampler was equipped with two valves and their configuration has been described elsewhere (Khan et al., 2012). A Surveyor LC pump (Thermo Fisher Scientific, San Jose, CA, USA) was used to load the sample from the 1 mL loop on to an on-line SPE Oasis HLB column (2.1 × 20, 15 μm; Waters, Ireland), where it was enriched using water. After 1.5 min, the valve was switched and the Accela pump (Thermo Fisher Scientific, San Jose, CA, USA) was used to extract the compounds from the Oasis column using a gradient flow of methanol. The gradient program for the Accela and Surveyor pumps is detailed in Tables S1 and S2, respectively, in the Supplementary Information. Following elution from the Oasis column, the analytes were separated on an analytical column (Thermo Hypersil GoldAQ, 50 × 2.1 mm, 5 μm + guard column), using the gradient program