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Liquid chromatography–mass spectrometry as a tool for wastewater-based epidemiology: Assessing new psychoactive substances and other human biomarkers

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ABSTRACT

Wastewater-based epidemiology (WBE) started to develop significantly in the last 8 years due, in part, to the advance of liquid chromatography–mass spectrometry (LC–MS). Its initial objective — to estimate the consumption of illicit drugs — has been expanded to new psychoactive substances (NPS) and other human biomarkers of health, lifestyle and disease. The purpose of this review is to introduce recent methods and outstanding challenges in the application of LC–MS to these new targets, including target, suspect and non-target screening and, outline the workflows developed for discovering metabolites of NPS and biomarkers. Further, we discuss a number of specific methodological challenges that also deserve scrutiny in future research.

1. Introduction

Wastewater-based epidemiology (WBE) follows from the principle of considering untreated wastewater, which end-up in the municipal sewage system, as a huge urine and stools pool where the unaltered compound and/or metabolic residues of any substance ingested in the human body or excreted as a part of catabolic reactions are present [1–11]. WBE was conceived by Daughton in 2001 [12] and implemented using cocaine as a model compound by Zuccato et al. (2005) [13]. Cocaine and its main urinary metabolite (benzoylecgonine, BE) were measured by liquid chromatography–mass spectrometry (LC–MS) in water and wastewater. Since then, WBE and LC–MS have been strongly linked so that, the evolution of the former has marched hand in hand with the instrumental development of the latter and the establishment of their new platforms and improved workflows [1,6,7]. This methodology — schematized in Fig. 1 — has turned into an important tool for monitoring patterns and trends of illicit drug consumption in communities that allows to track human habits and lifestyle as well as the associated outcomes on health, education and crime [11]. Sewage analysis CORe group Europe (SCORE) was established in 2010 to collaborate on international studies comparing illicit drug use between major cities and to evaluate the analytical procedures to their determination in wastewater [14]. WBE is also the target of several European actions including the COST Action ES1307 "Sewage biomarker analysis for community health assessment" and other similar or complementary initiatives [14]. The European Monitoring Centre for Drug and Drug Addiction (EMCDDA) and other international governmental agencies, such as the United Nations Office on Drugs and Crime (UNODC), have shown interests in exploring the potential of wastewater analysis for enhancing drug monitoring in Europe [15,16]. Recently, and already for several years, EMCDDA supports a Europe-wide demonstration program "Wastewater analysis and drugs — a European multi-city study" that includes year after year an increasing number of cities [15]. The results are released through an innovative interactive map and chart-based tool

Abbreviations: BE, benzoylecgonine; BOD, biological oxygen demand; COD, chemical oxygen demand; DDA, data dependent acquisition; DIA, data independent acquisition; EMCDDA, European Monitoring Centre for Drug and Drug Addiction; ESI, electrospray ionization; HLB, hydrophilic–lipophilic balanced; HR-MS, high resolution; LC–MS, liquid chromatography–mass spectrometry; LLE, liquid–liquid extraction; LR, low resolution; N, nitrogen; NPS, new psychoactive substances; P, phosphorous; PI, positive ionization; QqQ, triple quadrupole mass spectrometer; QqTOF, quadrupole time-of-flight; QTRAP, quadrupole linear ion-trap; SPE, solid phase extraction; SRM, selected reaction monitoring; TPs, transformation products; t_R, retention time; UHPLC, ultra-high performance liquid chromatography; WBE, wastewater-based epidemiology; XICs, extracting ion chromatograms.

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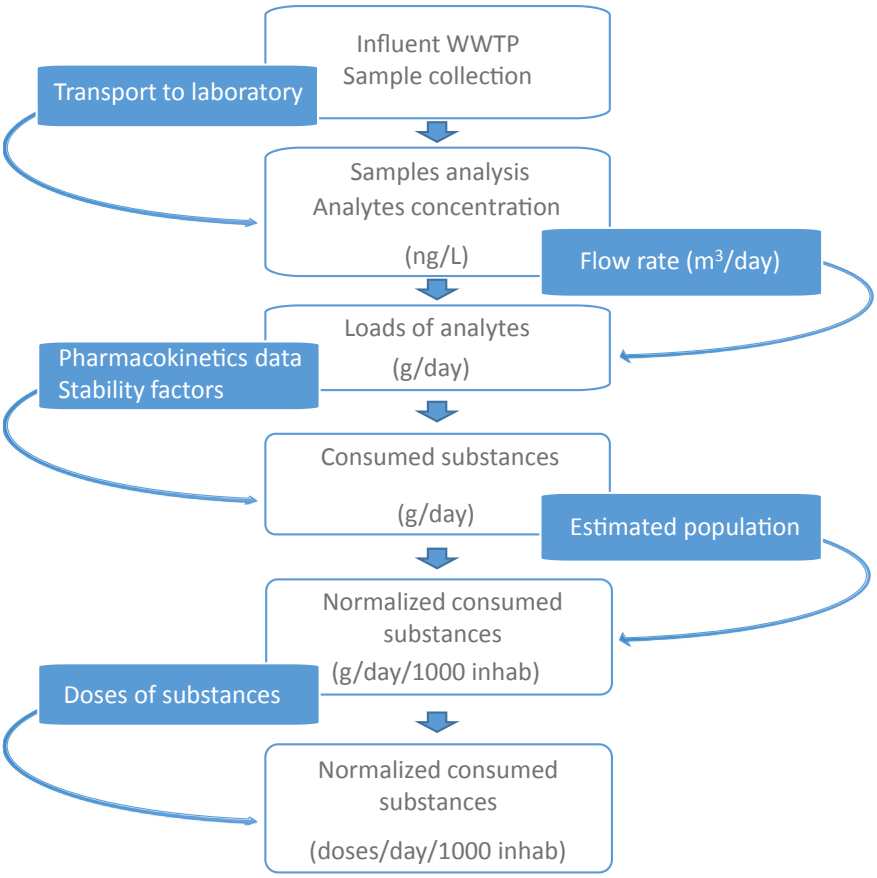

Fig. 1. Scheme of the workflow in wastewater-based epidemiology.

allowing the user to look at geographical and temporal patterns and zoom in on results per city. These are just few highlights to remark the interest of this approach, fully based on LC–MS determination.

WBE is multi-disciplinary in nature, since it includes from the sewer engineering to analytical chemistry, environmental toxicology, biology, pharmacology, public health, forensics, and so on. A number of reviews have covered, totally or in part, the topic of WBE. Most of them were focused on how to calculate drug consumption from wastewater analysis and the reliability of the estimation [8,11,17–20]. Other large group of reviews evaluate the uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers [2,3,18,21]. A number of original research articles that compared illicit drug use in increasing number European cities through sewage analysis complemented previous reviews [9,22]. This contrasts with the scarce reviews that cover the analytical part of these determinations. Only one recent review has tacked the most-recent literature available (mostly from the last 5 years) on the mass spectrometric determination of biomarkers of traditional illicit drug in wastewater with particular emphasis on the different analytical strategies applied [23], which is only a small part of WBE.

Recent advances in LC–MS have extended WBE to estimate consumption, use or exposure to different licit and illicit drugs — specially new psychoactive substances (NPS) — or even human biomarkers of contaminant exposure or population health and disease [5,10]. In a near future, WBE will be envisaged as a promising tool for the real-time collection of exposure/effects data that would reflect the overall average health of entire communities. These achievements are related to the advances on LC–high resolution (HR)-MS including the recently developed schemes based on *suspected screening* and *non-target* searching that open a new horizon to detect new compounds, including biomarkers and identify not-yet-reported metabolites and degradation products [24,25]. We critically address the current state-of-the-art and recent advances in LC–MS and LC–HR-MS to determine NPS and biomarkers in WBE and their pros and cons. In addition, an insight into the technologies that need further exploration and advancement for effective discovering and detection of a wider range of biomarkers, in order to enlarge the scope of WBE, is provided.

2. LC–MS for real-time collection of exposure/consumption data in WBE

2.1. New psychoactive substances (NPS)

To the moment, WBE has been widely applied to evaluate the illicit drugs use patterns. Several reviews — led by those published Postigo et al. [19] and Castiglioni et al. [20] in 2008 cover this topic. Van Nuijs et al. [11] detailed the illicit drug consumption estimations derived from wastewater analysis published until 2010. Hernandez et al. [23] emphasised on the different mass spectrometry strategies applied to identify and quantify illicit drug biomarkers in the last 5 years. In our review, the large number of publications evaluating traditional illicit drug consumption in different cities of the world for the last 5 years is compiled in the supplementary content (Table S1 in supplementary content) to offer together with the previous reviews, a comprenhensive overview to the reader. The analytical protocols are already well-established for those considered “traditional illicit drugs”. Nowadays, the pattern of