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Tracing methamphetamine and amphetamine sources in wastewater and receiving waters via concentration and enantiomeric profiling

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ABSTRACT

Wastewater analysis is a promising approach to monitor illicit drug abuse of a community. However, drug use estimation via wastewater analysis may be biased by sources other than abuse. This is especially true for methamphetamine and amphetamine as their presence in wastewater may come from many sources, such as direct disposal or excretion following administration of prescription drugs. Here we traced methamphetamine and amphetamine sources via concentration and enantiomeric profiling of the two compounds from black market to receiving waters. Methamphetamine in wastewater was found to predominantly arise from abuse, proving the feasibility of using wastewater analysis for estimating its consumption in China. Amphetamine abuse was previously considered negligible in East and Southeast Asia. However, we found that amphetamine was abused considerably (up to 90.7 mg/1000 inh/day) in a significant number (>20%) of major cities in China. Combined concentration and enantiomeric profiling also revealed direct disposal into receiving waters of methamphetamine manufactured by different processes. These findings have important implications for monitoring of and law enforcement against methamphetamine/amphetamine abuse and related crimes in China and abroad.

HIGHLIGHTS

- Methamphetamine and amphetamine sources were traced via concentration and enantiomeric profiling.
- Methamphetamine in Chinese wastewater was found to predominantly arise from abuse.
- Amphetamine was abused considerably in a significant number of major cities in China.
- Combined concentration and enantiomeric profiling revealed direct methamphetamine disposal into receiving waters.

1. Introduction

Amphetamine-type stimulants (ATS), including mainly amphetamine, methamphetamine, and ecstasy-group substances (e.g., 3,4-methylenedioxymethamphetamine), are the second most widely used class of drugs worldwide (after cannabis) (UNODC, 2015). East and Southeast Asia, with about one third of the global population, has some of the most established ATS markets in the world (Global SMART Programme, 2011, 2013, 2015). Methamphetamine (METH) is the primary ATS and its use continues to increase across the region. For example, METH seizure in China has roughly quadrupled from 6.15 t in 2008 to 25.9 t in 2014, far exceeding seizures of other drugs (Office of China National Narcotic Control Commission, 2009, 2015). Some countries also seized significant amounts of ecstasy pills (e.g., over 4 million in Indonesia in 2012) (Global SMART Programme, 2013). In contrast, no amphetamine (AMP)-related seizure, arrest, and manufacturing facility was recorded in the past 2–3 years (Global SMART Programme, 2011, 2013), indicating AMP abuse in the region was minor.

Traditional drug monitoring methods, based largely on population surveys, are time consuming and may be inaccurate (Zuccato et al., 2008). In the past decade, a new approach has emerged that estimates drug consumption by measuring drug concentrations in wastewater and taking into account population serviced, stability of drug residues, excretion rates, and wastewater volumes (Zuccato et al., 2005). This approach, being more objective and much less time-consuming (Zuccato et al., 2008), has been applied in many countries (e.g., Castiglioni et al., 2015; Du et al., 2015; Kim et al., 2015; Lai et al., 2013; Metcalfe et al., 2010; Nuijs et al., 2009; Thomas et al., 2012). While this approach represents a significant improvement, it also has uncertainties and biases. For example, drug release into wastewater may arise from sources other than its abuse (e.g., direct disposal; metabolism of other drugs), which may lead to significant biases. This is especially true for AMP

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and METH, as both drugs have legal medical uses and can be excreted following administration of a number of medicines (Cody, 2002).

Most illicit drugs are chiral and exist in the form of two or more enantiomers (Kasprzyk-Hordern et al., 2010). Different manufacturing processes can yield illicit drugs of completely different enantiomeric compositions. For example, the Leuckart or reductive amination process that uses phenyl-2-propanone as a precursor yields racemic METH products, whereas the Emde or Nagai processes using ephedrine or pseudoephedrine as precursors yield solely S(+)-METH (Remberg and Stead, 1999). Furthermore, METH, AMP, and their precursor drugs are metabolized by the human body with characteristic enantioselectivity (Cody, 2002). Thus, comparing enantiomeric compositions has the potential to shed light on sources of chiral drugs. Chiral analysis linked the excessively high mass loads of MDMA in wastewater during a sampling campaign in Utrecht to direct MDMA disposal, demonstrating the potential of enantiomeric profiling for source tracing of illicit drugs (Emke et al., 2014). Using concentration and enantiomeric distribution of fluoxetine in raw wastewater and other information (e.g., prescription data), Petrie et al. (2016) demonstrated direct disposal of fluoxetine. In addition, the authors proposed a framework to differentiate consumed and nonconsumed loads in wastewater. However, the scheme could only apply to simple cases when the enantiomeric form of the drug in question is known, and there are no other sources of the parent drug and its metabolites. Such a framework does not apply to METH and AMP, as METH is produced in different enantiomeric forms by different routes. Furthermore, METH and AMP are also metabolites of many other pharmaceuticals (e.g., deprenyl, benzphetamine) (Cody, 2002), which complicates the source apportionment of METH and AMP in wastewater dramatically.

In this work, enantiomeric profiling of METH and AMP was expanded to METH drugs seized from suppliers, the urines of abusers, wastewater, and rivers across China. In addition to enantiomeric profiling, AMP and METH concentrations, as well as concentration ratios between the two drugs were also compared. Factors that might affect the concentrations and the enantiomeric compositions of METH and AMP in wastewater and rivers were fully discussed. The combined profiling approach yielded unique insights and unequivocally revealed different METH and AMP sources in wastewater and receiving waters in China. To our knowledge, this is the first report of simultaneous concentration and enantiomeric profiling of two closely related drugs throughout its cycle from the supply market to receiving waters.

2. Materials and methods

2.1. Sample collection

In total, 67 crystalline and 54 tablet samples were randomly picked for analysis from METH drugs seized in Heilongjiang, Beijing, Ningxia, Sichuan, Zhejiang, Hubei, Shandong, and Guangdong provinces. These provinces cover all the geographic regions of China. No sample of "Shenxian Shui", a mixed liquid drug that also contains METH, was collected. According to the Bureau of Narcotics Control (personal communication), seizure of this drug was negligible compared to those of crystalline and tablet METH. Furthermore, METH concentrations in this drug were very low (0.04–1.3%) (Zhu et al., 2014). Urine samples of METH abusers were collected in Shandong (21 samples) and Guangdong (31 samples) provinces in the first half of 2015 with the assistance of local rehabilitation centers, in accordance with a protocol approved by the ethics committee of Peking University and with the informed consent of the addicts (The ethics approval number is IRB00001052-16029). Time proportional composite influent wastewater samples were collected for two days (i.e., 2 samples) using autosamplers or manually from 19 STPs at 14 major cities across China in the summer of 2014 and 2015 (Fig. S1). Time proportional composite wastewater effluents (10 samples) were also collected from 5 STPs in Beijing, Guangzhou, and Shenzhen. Twelve and eight grab samples were collected in the summer of 2015 along Liangshui (LSR) and Shenzhen (SZR) rivers that flow through Beijing and Shenzhen, respectively (Fig. S2). The Liangshui River receives effluent from STPs BJ-2 and BJ-3, whereas the Shenzhen River receives effluent from STP SZ-1. Details of sample collections are available in Supplementary Content (Table S1, S2).

2.2. Sample preparation and analysis

Seized METH samples were dissolved in methanol (MeOH) to roughly 1 mg mL^{-1}, filtered using 0.22 μm centrifuge filters, and diluted 5000 and 1000 times for LC-MS/MS analysis of METH and AMP, respectively. Urine samples were first diluted by MeOH by a factor of 6, vortexed for 20s, and centrifuged for 1 min at 13000*g*. Aliquots of supernatants were spiked with deuterated internal standards and then further diluted 2 to 40 times by MeOH. Wastewater and river waters samples were pretreated using solid phase extraction. An Oasis HLB cartridge (60 mg, 3 mL, Waters, UK) was conditioned in sequence with 2 mL MeOH and 2 mL deionized water at pH = 7.5 (adjusted using ammonium hydroxide). Wastewater (50 mL) or river water (200 mL), filtered using a 0.45 mm glass fiber membrane and spiked with internal standards, was loaded to the cartridge at a flow rate of 1–2 mL min^{-1}. The cartridge was then rinsed using 5% MeOH solution, dried under vacuum, and eluted using 4 mL MeOH. The eluate was evaporated to dryness, redissolved in 200 μL MeOH, and further cleaned using a centrifugal filter.

Pretreated samples were analyzed using a UFLCXR-LC system (Shimadzu, Japan) coupled with a Chirobiotic V2 column (250 mm × 2.1 mm, 5 μm) (Sigma-Aldrich, UK) at an injection volume of 5 μL. Enantiomer separation was undertaken at 20 °C and a flow rate of 0.25 mL min^{-1}, under isocratic conditions with a mobile phase composed of MeOH, glacial acetic acid, and ammonium hydroxide (100:0.1:0.025, v/v). Baseline separation of both METH and AMP enantiomers was achieved (Fig. S3).

Concentrations of individual enantiomers were determined using an API 4000 triple quadrupole mass spectrometer (AB SCIEX, USA) equipped with an electrospray interface operating in positive ionization mode (Table S3). Enantiomeric fractions (EFs) were derived by dividing the S(+)-enantiomer concentrations by the summed concentrations of the two enantiomers. EFs greater and lower than 0.5 indicate enrichment of S(+)- and R(−)-enantiomers, respectively. Method quantification limits (MQLs) of METH and AMP were 2 ng L^{-1} for wastewater and 0.5 ng L^{-1} for river water, respectively. Recoveries and matrix effects of the enantiomers were >92% and 84%, respectively. Details of sample analysis and method validation are provided in Supplementary content (Tables S3–5).

2.3. Load and consumption estimation

The total daily mass loads of AMP and METH at a specific STP were estimated using the following equation:

$$\text{Load}\left(\frac{\text{mg}}{1000\ \text{inh}\cdot\text{d}}\right)=\frac{\text{Conc.}\left(\frac{\text{ng}}{\text{L}}\right)\times\text{influent flow}\left(\frac{\text{L}}{\text{d}}\right)}{\frac{\text{Population served}}{1000}}\times\frac{1}{10^6}\left(\frac{\text{mg}}{\text{ng}}\right)$$

where conc. represents summed concentrations of the two enantiomers. The contribution of AMP abuse to the total load of AMP was derived by subtracting the contribution of METH metabolism:

$$\text{Load}_{\text{AMP abuse}}=\text{Load}_{\text{AMP total}}-\text{Load}_{\text{METH}}\times 0.07$$

where 0.07 represents the upper bound of the concentration ratio of AMP and METH in wastewater following METH abuse (details provided in below sections). Consumption of AMP and METH was back-calculated from loads of abuse by multiplying correction factors (2.77 and 4.4,