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Refining the excretion factors of methadone and codeine for wastewater analysis — Combining data from pharmacokinetic and wastewater studies

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ABSTRACT

Analysing drug residues in wastewater (wastewater analysis) to monitor the consumption of those drugs in the population has become a complementary method to epidemiological surveys. In this method, the excretion factor of a drug (or the percentage of drug metabolites excreted through urine) is a critical parameter for the back-estimation of the consumption of a drug. However, this parameter is usually derived from a small database of human pharmacokinetic studies. This is true for methadone and codeine, the two most commonly used opioids and also common substances of abuse. Therefore, we aimed to refine the current excretion factors used for estimating methadone and codeine by analysing published data from the literature on the excretion of methadone, its main metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and codeine. Our review included both human drug pharmacokinetic studies and wastewater analysis studies. We found that while the commonly used excretion factor of methadone (~27.5%) was relatively accurate, the excretion factor of EDDP, a better biomarker for methadone consumption in sewer epidemiology, should be twice that of methadone (i.e. 55%) instead of the current equal or half values. For codeine, the excretion factor should be ~30% instead of 63.5% or 10% as previously used in wastewater analysis studies. Data from wastewater analysis studies could be used in this way to refine the excretion factors of the drugs of interest.

1. Introduction

Since its first application in 2005, wastewater analysis (or sewage epidemiology) has become an accepted approach for monitoring population drug use (Castiglioni et al., 2014). Advances have been made in reducing the overall uncertainty of the final drug consumption estimate by improving the sampling procedure and using new analytical methods to reduce the uncertainties in back-calculating population drug use (Castiglioni et al., 2013, 2014). However one important contributor to the uncertainty of the final back-estimate of drug use still requires research attention, namely, the excretion factors of target substances (Bruno et al., 2014; Castiglioni et al., 2014). The excretion factor of a drug in sewer epidemiology is the fraction of the consumed dose that is excreted as its metabolites or unchanged parent compound in the urine and feces after use. This factor is critical in ensuring good drug use estimates but it has usually been based on a surprisingly small number of human pharmacokinetic studies, usually involving small numbers of participants (Bruno et al., 2014).

Khan and Nicell (2011) reported that early studies of wastewater epidemiology relied on the excretion factors first used by Zuccato et al. (2008). These excretion factors were largely based on "excretion estimates arising from either single studies of limited scope and/or studies of limited applicability" (Khan and Nicell, 2011). In order to increase their applicability and reliability, Khan and Nicell attempted to refine the excretion factors for several drugs including cocaine, heroin and MDMA (Khan and Nicell, 2011), and methamphetamine, amphetamine and THC in a subsequent study (Khan and Nicell, 2012). These two studies concentrated on major illicit drugs, which have been the target of the majority of sewer epidemiology studies to assess the prevalence and trends in the use of these drugs in different populations worldwide (e.g. Khan et al., 2014; Lai et al., 2013; Ort et al., 2014; Thomas et al.,

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2012). At the same time, Melis et al. (2011) also reviewed the available knowledge on human metabolism of the major illicit drugs but did not draw any conclusions or recommendation on their excretion factors.

As sewer epidemiology becomes more routinely used for drug consumption monitoring, it needs to expand the target monitoring to licit drugs which are susceptible to misuse (Hernandez and Nelson, 2010). Among those of great interest are methadone and codeine, two popular prescription opioids, which are subject to misuse (UNODC, 2015). Methadone is a potent synthetic opiate receptor agonist that is primarily used as an agonist maintenance treatment for opiate dependent individuals. It can also be used for chronic pain treatment. It is the most commonly used drug around the world to treat opiate dependent patients (EMCDDA, 2009). Due to its opioid agonist effects, however, methadone is also susceptible to misuse and diversion, both in closed communities (e.g. prisons) as well as in the wider community (Nicholas et al., 2011; AIHW, 2011). Codeine is the most common opioid which is used as pain reliever and can be purchased as an over-the-counter pharmaceutical in many countries (Tobin et al., 2013). Abuse of codeine may lead to fatal overdose, the rate of which has increased in Australia (Roxburgh et al., 2015).

The potential of extramedical use of methadone and codeine in the community suggests that we need to find excretion factors to more accurately estimate their consumption from wastewater analysis. It is even more important for the case of methadone where its main metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), has been identified as a suitable marker for monitoring methadone consumption (Been et al., 2015) but very few studies have used this compound to back-estimate the amount of methadone consumed (Baker et al., 2014; Been et al., 2015; van Dyken et al., 2014) even when the data of EDDP was also available (Postigo et al., 2011). Previous wastewater studies have applied different excretion factors to estimate the consumption of methadone (e.g. Postigo et al., 2011, Been et al., 2015) and codeine (e.g. Baker et al., 2014, Kim et al., 2015, van Dyken et al., 2014). More interestingly, two studies on codeine consumption found that the wastewater estimates did not match drug consumption statistics (Baker et al., 2014; Kim et al., 2015).

This study aimed to review the pharmacokinetic and wastewater analysis studies that involved the excretion of methadone and codeine. The intended outcome of the review was the derivation of new excretion factors that more accurately estimate methadone and codeine. These were tested on a set of wastewater data gathered in South East Queensland, Australia.

2. Methods

2.1. Data collection

The Web of Science electronic database was searched for studies related to methadone and codeine. The two main search categories comprised (i) methadone and codeine monitoring using wastewater, namely: methadone, EDDP, codeine, wastewater/sewage, excretion factor; and (ii) pharmacokinetics of those drugs, namely: methadone, EDDP, codeine, human, excretion, urine/urinary, percentage. Our search was limited to studies published in English. Then a further screening of abstracts identified the studies which could be used in our analysis.

To provide the basis for a new value of the excretion factor, we also looked specifically for studies which compared estimated consumption with actual consumption data or official record data. These were identified through full-text review of the papers gathered from previous screening.

2.2. Estimation of excretion factors

The data from the literature were analysed to identify: (i) the current excretion factors for methadone and codeine; (ii) the ratio of EDDP/methadone in urine and wastewater samples; and (iii) the gap between previous estimates and official consumption data.

The new excretion factors were then estimated by selecting the values which could fill the gap between the estimates and the official data and, in case of methadone, match the ratio of EDDP/methadone found in urine and wastewater samples.

2.3. Application to real data set

The newly derived excretion factors were then applied to a set of wastewater monitoring data. The wastewater was sampled between 3rd May 2011 and 5th June 2012 (n = 344 sampling days) at a wastewater treatment plant (WWTP) serving a major urban catchment of approximately 230,000 people in Southeast Queensland, Australia. A continuous-flow proportional sampling technique was used and daily 24 h-composite samples (6 AM–6 AM) were collected. Samples were collected at 4 °C. Samples were acidified to pH 2 and then frozen until analysis. Details of the analytical methods and back calculation of the involved chemicals were previously presented in Kim et al. (2015), Lai et al. (2015) and van Dyken et al. (2014). Briefly, filtered samples (1 mL) were spiked with the corresponding mass-labelled analogues of the target compounds. Then, the samples together with six-point calibration standards were analysed using liquid chromatograph (Shimadzu, Nexera UHPLC system, Kyoto, Japan) coupled with tandem mass spectrometry (AB-SCIEX QTRAP®5500, Ontario, Canada) in direct injection mode. Concentrations of the compounds were quantified taking into account the correction of the mass-labelled compounds for matrix effects and instrumental variation.

In every batch of sample analysis, procedural blank samples, duplicate samples, and samples spiked with the native EDDP, methadone and codeine were included as the quality assurance and control (QA/QC) of the analysis. There was no contamination with any of the analytes of interest found in the blank samples. The difference (relative standard deviation, %) between duplicate samples was on average 6.9% for codeine, 5.7% for methadone, and 5.6% for EDDP. The recovery of the native chemicals spiked in the samples was on average 86% for codeine, 79% for methadone, and 81% for EDDP.

Official data for the consumption of methadone and codeine for the validation were extracted from national statistics reports. The number of methadone doses dispensed in 2012 for Queensland was extracted from AIHW (2013) and the average dose value indicated by Medicines Regulation and Quality Unit, Department of Health of Queensland according to their annual review. The total sale of codeine for 2013 in major cities of Queensland (prescription and over-the-counter combined) reported by Gisev et al. (2016) was used for codeine.

3. Results and discussion

3.1. Literature search results

We found 44 studies of wastewater analysis that involved the measurement or estimation of methadone, EDDP and/or codeine. A summary of those studies is presented in Table 1. It is shown that methadone and EDDP have been monitored in wastewater across the globe but mostly in Europe along with other illicit drugs because use of methadone is closely related to illicit opioid use. Other studies were conducted in Australia, China, and the USA. Codeine was slightly less frequently monitored, partially because as a drug available over-the-counter it attracts less attention from researchers doing wastewater analyses of illicit drugs.

The search also identified 14 papers reporting the urinary measurement of both methadone and EDDP (Table 2) which could provide the estimates of the ratio of EDDP/methadone. And the detailed review of the 44 wastewater studies mentioned above revealed 6 studies reporting drug consumption estimates for methadone and codeine