Forensic Science International 285 (2018) 58–64

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Post-mortem quetiapine concentrations in hair segments of psychiatric patients — Correlation between hair concentration, dose and concentration in blood

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ARTICLE INFO

Article history:
Received 25 September 2017
Received in revised form 9 January 2018
Accepted 27 January 2018
Available online 3 February 2018

Keywords:
Quetiapine
Post-mortem toxicology
Segmental hair analysis
Antipsychotics
UHPLC–MS/MS

ABSTRACT

Drug analysis in hair is useful when seeking to establish drug intake over a period of months to years. Segmental hair analysis can also document whether psychiatric patients are receiving a stable intake of antipsychotics. This study describes segmental analysis of the antipsychotic drug quetiapine in post-mortem hair samples from long-term quetiapine users by ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) analysis. The aim was to obtain more knowledge on quetiapine concentrations in hair and to relate the concentration in hair to the administered dose and the post-mortem concentration in femoral blood.

We analyzed hair samples from 22 deceased quetiapine-treated individuals, who were divided into two groups: natural hair colour and dyed/bleached hair. Two to six 1 cm long segments were analyzed per individual, depending on the length of the hair, with 6 cm corresponding to the last six months before death. The average daily quetiapine dose and average concentration in hair for the last six months prior to death were examined for potential correlation. Estimated doses ranged from 45 to 1040 mg quetiapine daily over the period, and the average concentration in hair ranged from 0.18 to 13 ng/mg. A significant positive correlation was observed between estimated daily dosage of quetiapine and average concentration in hair for individuals with natural hair colour ($p = 0.00005$), but statistical significance was not reached for individuals with dyed/bleached hair ($p = 0.31$). The individual coefficient of variation (CV) of the quetiapine concentrations between segments ranged from 3 to 34% for individuals with natural hair colour and 22–62% for individuals with dyed/bleached hair. Dose-adjusted concentrations in hair were significantly lower in females with dyed/bleached hair than in individuals with natural hair colour. The quetiapine concentrations in post-mortem femoral blood and in the proximal hair segment, segment 1 (S1), representing the last month before death were also investigated for correlation. A significant positive correlation was observed between quetiapine concentrations in blood at the time of death and concentrations in S1 for individuals with natural hair colour ($p = 0.003$) but not for individuals with dyed/bleached hair ($p = 0.31$). The blood concentrations of quetiapine ranged from 0.006 to 1.9 mg/kg, and the quetiapine concentrations in S1 ranged from 0.22 to 24 ng/mg.

The results of this study suggest a positive correlation of quetiapine between both concentrations in hair and doses, and between proximal hair (S1) and blood concentrations, when conditions such as hair treatments are taken into consideration.

1. Introduction

Quetiapine is an atypical antipsychotic agent that has been used clinically since 1997 to treat schizophrenia, bipolar disorder, and major depressive disorder combined with an antidepressant [1]. The drug can be abused for its euphoric properties, and illicit

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https://doi.org/10.1016/j.forsciint.2018.01.020
0379-0738/

quetiapine use has been reported [1–4]. Quetiapine use has also been reported in drug-facilitated sexual assaults due to its sedative effect [5]. The therapeutic blood concentration of quetiapine ranges from 0.1 to 0.5 mg/L, the toxic concentration is 1 mg/L and fatal quetiapine poisoning has been reported at 1.9 mg/L and above [6]. The half-life of quetiapine in blood is approximately 5–7 h [6]. Quetiapine show minimal time-dependant post-mortem redistribution in femoral blood [7].

One way of analysing drug intake is by hair analysis, which offers the opportunity to measure months to years of drug exposure, depending on the hair length. These measurements may be useful for interpreting possible drug intoxication cases and discriminating between single exposure and long-term drug use [8,9]. Assessment of long-term medication is of particular interest in terms of chronic antipsychotic treatment, as segmental hair analysis can be used to investigate the compliance of patients with their medical treatment [10–13]. In segmental analysis, the individuals serve as their own controls because the concentration in one hair segment can be compared to the concentration in another segment from the same individual [14].

Reference values for antipsychotics in hair are valuable both for therapeutic drug monitoring and for forensic toxicology, and several studies have been published over the years on antipsychotics in hair [10–13,15–21]. However, the published literature lacks information on drug doses and related concentrations in hair for most antipsychotics [13]. Previous studies have reported quetiapine concentrations in hair ranging from 0.35 to 10.2 ng/mg for chronic antipsychotic treatment (n = 17) [21–24], 0.10 to 2.29 ng/mg in four 2 cm long segments for repeated administration (n = 1) [25], and 0.011 ng/mg for single-dose drug-facilitated sexual assault (n = 1) [5]. Drug doses and drug concentrations in hair can show a relationship, but determination of an oral daily dosage is not possible based on a concentration in hair [12,15,19,26–28]. This is due to many variables, such as sex, age, melanin binding, enzymatic activity, hair growth and hair treatment, which all cause high inter-individual variation at equal drug doses [12,15,26,27]. The number of controlled studies is also limited, and most studies have enrolled only small numbers of participants.

In the present study, quetiapine concentrations are assessed in hair segments of deceased mentally ill individuals. Our aim was to obtain more knowledge on post-mortem quetiapine concentrations in hair in relation to administered doses and post-mortem quetiapine concentrations in femoral blood. To our knowledge, only one other publication, by Binz et al. [21], has presented data on a correlation between quetiapine concentrations in hair and daily dosage.

2. Materials and methods

2.1. Chemicals and reagents

Reference standards of quetiapine and dibenzepine (internal standard) were obtained from Toronto Research Chemicals (Toronto, CA). The quetiapine purity was 98%. Acetonitrile, methanol and water of LC–MS grade were from Fisher Scientific (Leicestershire, UK). Formic acid (98–100%) was from Merck (Darmstadt, DE) and ammonium formate was obtained from Fluka (Buchs, CH) (≥97% purity).

2.2. Authentic samples

Cases were selected from the *SURVIVE* population: a Danish National forensic autopsy-based study of deceased individuals with diagnosed or suspected mental illness collected in the period from 2013 to 2015 [29]. The project has permission from the Danish National Ethics Committee. Consent for this research was collected from the next of kin for each subject. Cases (n = 22) that showed quetiapine in post-mortem femoral blood and/or that had a medical report confirming quetiapine treatment were selected for analysis if head hair was also available.

2.3. Estimated daily dosage of quetiapine

The project has permission to use the Danish medicinal drug register which contains data from all Danish pharmacies and hospital pharmacies. Data on prescription pick-ups were extracted. Daily quetiapine dose was estimated by multiplying the number of tablets picked up times the quetiapine amount in the tablet. This was averaged for the last six months prior to death.

2.4. Hair extraction

A previously published extraction method was used, with minor modification [30]. The volume of the extraction medium was increased from 200 to 500 μL to obtain relevant extract concentrations. Briefly, hair samples were aligned and cut into 1 cm segments (duplicate determinations). Two to six segments were analyzed depending on each individual's hair length. Segment 1 (S1) was the segment closest to the scalp. Approximately 10 mg of hair was weighed into Precellys tubes (Bertin Technologies, FR) and decontaminated with 1 mL 2-propanol for 2 min, twice with 500 μL purified water for 2 min, and then with 1 mL 2-propanol for 2 min. The last aqueous wash was analysed to check for external contamination. The hair was air dried overnight and six steel beads for pulverisation were added, along with 500 μL of an extraction medium consisting of methanol, acetonitrile, and 2 mM ammonium formate (25:29:46 v/v/v). The hair was pulverised (4 × 30 s at 6500 rpm) using a Precellys 24 ball mill (Bertin Technologies, FR) and incubated overnight at 37 °C. Extracts were filtered using brown Mini-Uniprep vials containing a PTFE filter (Whatman Inc., New Jersey) and diluted 1:1 with water before analysis. The injection volume was 10 μL. Dibenzepine was used as internal standard [30]. Samples containing quetiapine extract concentrations that exceeded the upper limit of quantification (ULOQ) were reanalyzed with control hair samples at low and high levels using a 1 μL injection volume. The multi method covered 100 drugs, including antipsychotics, antidepressants, illicit drugs, anticonvulsants, benzodiazepines, hypnotics, opioids and antihistamines [30]. In this study, quantitative results for only quetiapine are evaluated. Quantitative results for some of the other drugs are shown in Supplementary Table S1.

2.5. UHPLC-MS/MS conditions

Chromatographic separation was performed using an Acquity ultra-high-performance liquid chromatography (UHPLC) system (Waters Corporation, Milford, USA) with an Acquity UPLC® HSS C_{18} 150 mm × 2.1 mm, 1.8 μm column. Compounds of interest were detected with a Waters® TQ Detector tandem quadrupole spectrometer (Waters Corporation) with electrospray ionisation. Two multiple reaction monitoring (MRM) transitions were used for quetiapine: one for quantification (m/z 384 > 253) and one for qualification (m/z 384 > 221), both with a cone voltage of 40 V and collision energy at 22 and 38 eV, respectively. The dibenzepine internal standard was measured at one transition (m/z 296 > 251) with a cone voltage of 30 V and collision energy at 18 eV. Analytical parameters and procedures were as previously described by Montesano et al. [30].