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Invited critical review

Advances in detection of antipsychotics in biological matrices

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ABSTRACT

Measuring antipsychotic concentrations in human matrices is important for both therapeutic drug monitoring and forensic toxicology. This review provides a critical overview of the analytical methods for detection and quantification of antipsychotics published in the last four years. Focus lies on advances in sample preparation, analytical techniques and alternative matrices. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is used most often for quantification of antipsychotics. This sensitive technique makes it possible to determine low concentrations not only in serum, plasma or whole blood, but also in alternative matrices like oral fluid, dried blood spots, hair, nails and other body tissues. Current literature on analytical techniques for alternative matrices is still limited and often requires a more thorough validation including a comparison between conventional and alternative results to determine their actual value. Ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) makes it possible to quantify a high amount of compounds within a shorter run time. This technique is widely used for multi-analyte methods. Only recently, high-resolution mass spectrometry has gained importance when a combination of screening of (un)known metabolites, and quantification is required.

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Abbreviations: ACN, Acetonitrile; CSF, Cerebrospinal fluid; DBS, Dried blood spot; ECD, Electrochemical detection; GC, Gas chromatography; HFBA, Heptafluorobutyric acid; IS, Internal standard(s); LC, Liquid chromatography; LC–MS/MS, Liquid chromatography–tandem MS; LLE, Liquid–liquid extraction; MS, Mass spectrometry; MeOH, Methanol; MTBE, Methyl-*tert*-butyl ether; MEPS, Micro-extraction by packed sorbent; MRM, Multiple reaction monitoring; MSTFA, N-methyl-N-(trimethylsilyl)trifluoroacetamide; PP, Protein precipitation; SIM, Selected ion monitoring; SPE, Solid-phase extraction; TDM, Therapeutic drug monitoring; TFAA, Trifluoroacetic anhydride; TMS, Trimethylchlorosilane; UHPLC, Ultra-high performance liquid chromatography; UV, Ultraviolet detection.

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1. Introduction

Antipsychotic drugs are widely used to treat psychotic symptoms within the context of schizophrenia, schizo-affective, schizophreniform, bipolar or psycho-organic disorders [1]. To date, 64 different compounds are classified as antipsychotics according to the World Health Organization. For about 70% of these antipsychotics, analytical methods are described in human matrices.

Measuring antipsychotic concentrations can be important in different circumstances. For instance, therapeutic drug monitoring (TDM) is recommended for almost all antipsychotics. Most of these drugs show narrow therapeutic ranges with a high risk for toxic side effects. A high interindividual variability in kinetics is seen and the pharmacological effects are concentration-dependent. Measuring concentrations of antipsychotics in serum or plasma can aid in optimizing therapy, explaining adverse effects, non-response, pharmacokinetic interactions and poor compliance [2].

In forensic cases different matrices are often provided. Whenever possible, blood is the preferred specimen. Antipsychotics are one of the psychoactive substances which are routinely screened for to determine the cause of death [3]. However, antipsychotic concentrations in post-mortem specimens can change, which makes interpretation of drug concentrations highly challenging. First, autolysis of cells can result in residual enzymatic activity which causes further metabolism of drugs. During putrefaction, bacteria invade the body and degrade the tissues. These degradation products can impede identification and quantification. Trifluoperazine, flupenthixol and chlorpromazine undergo putrefactive degradation in bacteria-contaminated liver tissue, while also olanzapine degrades due to oxidation. During autolysis and putrefaction, redistribution of drugs from tissues to blood can occur. Antipsychotics which are basic drugs with a high lipophilicity and a large volume of distribution are likely to be susceptible to post-mortem redistribution. Saar and colleagues compared post-mortem blood concentrations measured upon admission to the mortuary and at autopsy, to study the effect of time on the redistribution of antipsychotics. Most of these drugs showed a significant change in concentrations going from an average increase of 112% (for chlorpromazine and olanzapine) to an average decrease of −43% (for paliperidone). Only haloperidol, quetiapine and risperidone were found to have a low risk for post-mortem redistribution [4,5]. Due to the difficult interpretation of post-mortem blood concentrations, it is preferable to prove the presence and even quantify the substance in other specimens too. The type of specimen is depending on the availability and the analyte found in the case. On the other hand, when blood is not provided, quantification in other matrices like liver, urine, gastric content or kidney can be desired [3].

Reviews of the analytical methods for detection of antipsychotics were published by Zhang et al. [6] and Saar et al. [7]. Saar et al. focused on the analytical methods using liquid chromatography (LC) coupled to a mass spectrometer (MS) or tandem MS (LC–MS/MS), while the other review published in 2008 included all analytical methods described for analysis of antipsychotics between 1981 and 2007. As was already highlighted, interest in matrices other than blood, serum or plasma, has grown in the last 2 decades [7].

Our aim was to provide an overview of the analytical methods for detection of antipsychotics in all human matrices published between 2010 and September 2014. This includes both gas chromatography (GC) and LC methods using different detectors. Both Web of Science and Pubmed were searched for English publications using general key words like 'antipsychotic drugs', 'neuroleptics' and 'psychotropic drugs' but also the individual antipsychotics, in combination with the key word 'chromatogr*'. Table 1 provides an overview of all LC-methods and Table 2 summarizes all GC-methods for analysis of antipsychotics published within the last 4 years.

2. General considerations

In a clinical setting antipsychotic concentrations are measured in serum or plasma. There is no consensus about the use of plasma or serum. According to the AGNP-TDM Expert Group Guidelines experimental data which clearly indicate differences in the drug concentrations are lacking. The few available comparisons indicate that values obtained for serum or plasma can be used interchangeably [2].

The sample volumes used in the analytical methods for serum, plasma or whole blood have been decreased in the last few years. Between 2010 and September 2014 the mean sample volume was 0.2 ml (range 0.03–1 ml). Due to the low dosage and the high distribution volume of most of the antipsychotics, blood concentrations are rather low. This was the main reason why most of the older methods used larger blood volumes of 0.5 or 1 ml [7]. The decrease in sample volume can be due to the availability of more sensitive analytical techniques, but also sample preparation techniques needing smaller sample sizes like micro-extraction by packed sorbent (MEPS).

Whole blood, other body fluids and human tissue are especially interesting for forensic purposes. Whole blood is most frequently analyzed in forensics since serum or plasma is often not available due to lysis of cells. Since more sensitive methods became available, interest in alternative matrices for measuring antipsychotics for both forensic and TDM purposes has increased. At this moment, antipsychotics can be quantified in dried blood spots (DBS), hair, nails and cerebrospinal fluid (CSF).

Not only in a forensic setting but also in the psychiatric population, alternatives like DBS, hair, nails, oral fluid and urine can aid in measuring antipsychotics without the need for invasive sampling techniques like blood withdrawal. Oral fluid and urine have always been interesting matrices since they can be easily collected without the need for trained staff. Especially in acute situations, like forced admission to a psychiatric hospital, these specimens are attractive to measure antipsychotic concentrations. However, most of the publications about urine or oral fluid are attempts to validate analytical methods previously used for serum or plasma. Still, most of these studies have to conclude that both matrices are only interesting for screening purposes [7].

3. Advances in sample preparation

3.1. Conventional matrices

For the analysis of drugs in biological samples, sample pretreatment is a crucial step. For the conventional matrices like serum, plasma and whole blood 4 major sample pretreatment techniques are described: liquid–liquid extraction (LLE), solid-phase extraction (SPE), protein precipitation (PP) and direct injection.

LLE, an inexpensive technique which is based on the relative solubility in 2 immiscible fluids, is frequently used. This easy to perform sample clean-up is highly efficient, due to the lipophilic properties of the antipsychotics [1,8]. LLE is still the most frequently used sample preparation. However, there is no consensus as to which extraction solvent results in the highest recovery. Many different extraction solvents are described, of which ethyl acetate, methyl-*tert*-butyl ether (MTBE), butyl acetate and diethylether are used most often. The choice for an extraction solvent is based on the obtained recovery, which should be acceptable for all compounds included in the method, and based on practical considerations. Some authors even compared a lot of different extraction solvents during method development [9,10].

Although SPE results in a better specificity, cleaner extracts and the procedure can be automated, the technique is more expensive and time-consuming. As can be seen in Tables 1 and 2, SPE is used less frequently in comparison to LLE in the last 4 years. MEPS, a similar technique, is also described. This is a miniaturized SPE using a gas-tight syringe as extraction device. Only a few microliters of elution solvent is needed and coupling to analytical instruments is possible [11–13].