European Journal of Pharmaceutical Sciences 75 (2015) 25–39

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Review

Dried blood spots for monitoring and individualization of antiepileptic drug treatment

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ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 8 April 2015
Accepted 9 April 2015
Available online 17 April 2015

Keywords:
Therapeutic drug monitoring
Dried blood spots
Antiepileptic drugs
Clinical validation

ABSTRACT

Therapeutic drug monitoring (TDM) is a multi-disciplinary clinical specialty used for optimization and individualization of drug therapy in the general and special populations. Since most antiepileptic drugs (AEDs) are characterized by pronounced intra- and inter-individual variability, it can be especially valuable as an aid for dosing adjustments in patients with epilepsy. Dried blood spots (DBS) sampling technique is recognized as a suitable alternative for conventional sampling methods as TDM interventions should be applied in the most cost-effective, rational and clinically useful manner. In the present review we summarize the latest trends and applications of DBS in TDM of epilepsy. Quantification of AEDs in DBS was employed in various clinical settings and has been already reported for phenobarbital, phenytoin, valproic acid, clonazepam, clobazam, carbamazepine, topiramate, rufinamide, lamotrigine, 10-hydroxy-carbazepine and levetiracetam. The major limitation of the published studies are restricted evaluation of critical parameters such as the impact of spotted blood volume, spot homogeneity and haematocrit effect, limited clinical validation and non-established correlations between the DBS and plasma concentrations of AEDs. Standardization of critical technical aspects for appropriate sampling, sample preparation and validation of the analytical procedures for quantification of the drugs, as well as appropriate interpretation of the results are the fields which should get more attention in upcoming studies. Limited data on clinical validation and the fact that this technique has been used in practice only for a few AEDs makes the routine implementation of TDM of AEDs using DBS method a big challenge that should be faced by the pharmaceutical scientists in the future.

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http://dx.doi.org/10.1016/j.ejps.2015.04.008
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1. Introduction

Therapeutic drug monitoring (TDM) is a multi-disciplinary clinical specialty aimed at improving patient care by individually adjusting the dose of drugs for which clinical experience or clinical trials have shown it improved outcome in the general or special populations. It can be based on *a priori* demographic, clinical and pharmacogenetic information, and/or on the *a posteriori* measurements of drug blood concentration (pharmacokinetic monitoring) and/or biomarkers (pharmacodynamic monitoring) (IATDMCT, 2013). Antiepileptic drugs (AEDs) are a group of drugs used to decrease the frequency and/or severity of seizures in people with epilepsy and are characterized with extensive pharmacological and structural diversity (Bromfield et al., 2006). The rationale of employment of TDM in everyday clinical practice depends on their pharmacokinetic properties, especially on their intra- or inter-individual variability. Thus, TDM was initiated for a number of AEDs and used to establish optimal therapy regimens for individual patients (Patsalos et al., 2008).

First generation of AEDs including phenytoin, phenobarbital, carbamazepine and valproic acid is characterized by pronounced inter-individual variation in pharmacokinetics and a narrow therapeutic range (Johannessen and Tomson, 2002). For these AEDs TDM has been a common practice to guide dosage adjustment for a particular patient to achieve a serum drug concentration within the reference range at which most patients are expected to exhibit an optimal clinical response (Patsalos et al., 2008). On the other hand, there is some uncertainty about the utility of TDM regarding the second and third generation of AEDs which entered the market between 1990 and 2012. These drugs are characterized by more predictable pharmacokinetics and a substantial lack of documented correlation between drug concentration and drug effects (Johannessen and Tomson, 2006; Patsalos and Berry, 2012). Despite these characteristics TDM is a tool that can guide clinicians to provide effective and safe antiepileptic therapy in individual patient, to verify the drug compliance and to prevent and manage drug interactions, overdoses and toxicity (Patsalos et al., 2008).

Collecting biological samples for drug concentration measurements is the key component for effective TDM (Gross, 2001). In clinical practice, AED concentration measurements are usually performed in serum or plasma. Additionally, samples of whole blood, saliva, dried blood spots, tears, hair, sweat, cerebrospinal fluid and breast milk have been investigated (Johannessen and Landmark, 2008). Nowadays the idea of using an alternative specimen employing non-invasive and patient friendly techniques is becoming even more attractive with the development of sensitive analytical methods. Alternative specimens, appropriate for TDM, that are simple for collection from a patient perspective are saliva and DBS (Krasowski and McMillin, 2014).

DBS sampling, where blood is obtained via a finger-prick by the patients themselves or by medical personnel could be a convenient replacement for venous blood sampling for most AEDs. The use of DBS has been extensively discussed in the literature (Edelbroek et al., 2009; Li and Tse, 2010; Spooner et al., 2009). Feasibility of using DBS as a sampling technique has been thoroughly reviewed recently. However, so far none of these reviews has focused specifically on the use of DBS sampling for TDM in epilepsy.

In this paper we review the application of DBS as an alternative for venous and saliva samples for TDM of AEDs. We discuss the advantages, restrictions and key technical aspects that are relevant for practical employment of DBS method in everyday clinical practice compared to the conventional sampling techniques. We also review the published literature on existing DBS analytical methods for AEDs and discuss clinical implications and future perspectives of the implementation in TDM of epilepsy.

2. Therapeutic drug monitoring in epilepsy

TDM in epilepsy is very complex. Due to the episodic nature of the condition assessment of the clinical efficacy of AEDs is especially challenging as it is difficult to assess if the patient is responding to the therapy or is just free of seizures. Additionally, many times there are difficulties to differentiate clinical symptoms and signs of toxicity. The main assumption in TDM is that clinical effects correlate better with the drug concentration than with the dose (Patsalos et al., 2008).

Initially TDM was employed in clinical practice for the first generation of AEDs due to the complex and variable pharmacokinetics (Neels et al., 2004). The main pharmacokinetic parameters of AEDs are given in Table 1. Phenytoin is one of the earliest examples of drugs for which TDM is essential because of its narrow therapeutic window, high degree of protein binding, and nonlinear pharmacokinetics (Richens, 1979). Moreover, valproic acid is among AEDs most frequently reported for intoxications and monitoring of free valproic acid concentration can be helpful in identifying concentration related adverse effects (Bronstein et al., 2011). Carbamazepine, ethosuximide, phenytoin, and primidone are also considered good candidates for TDM since, in general, the first generation AEDs have significant inter-individual variability in pharmacokinetics and a narrow therapeutic window with toxicity and neurological side effects being a common problem (Perucca, 2005). Inter-individual and intra-individual variability in pharmacokinetics is a result of genetic factors, patient age, specific physiological conditions, associated diseases and drug–drug interactions. Genetic polymorphisms in drug metabolizing enzymes are of particular relevance for the first generation of AEDs. Genetic polymorphisms have been identified for cytochrome P450 (CYP) 2C9 and CYP 2C19, enzymes that are crucial to explain the variability in drug response (Johannessen and Landmark, 2010; Perucca, 2005; Shastry, 2006). Additionally, carbamazepine, phenobarbital, primidone and phenytoin are strong inducers of liver drug-metabolizing enzymes, whereas valproic acid is an inhibitor of multiple CYP enzymes. As a result of pharmacokinetic interaction, serum concentrations of concomitant drugs can be decreased or increased (Johannessen and Landmark, 2010; Perucca, 2005). Most of these drugs are highly bound to plasma proteins. Consequently, monitoring of free plasma drug concentration is preferred, especially in clinical situations where protein binding is disturbed (Dasgupta, 2007; Jansen et al., 2012).

Generally, the second generation of AEDs has more favourable pharmacokinetics, wider therapeutic range, reduced interaction profile, better tolerability and fewer adverse effects than the first generation. The strongest evidence for routine TDM is for lamotrigine, oxcarbazepine (10-hydroxycarbazepine metabolite), stiripentol, tiagabine, and zonisamide, mainly due to inter-individual variation in clearance. Pharmacokinetic interactions involving second generation of AEDs include the enzyme inhibitors felbamate, rufinamide, and stiripentol and the weak enzyme inducers

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