Abstract

Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment and there are now 27 licensed AEDs in total for the treatment of patients with epilepsy. This has led to an increasingly widespread application of therapeutic drug monitoring (TDM) making AEDs among the most common medications for which TDM is performed. For the older first generation AEDs (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid) much data has accumulated in this regard. However, increasingly this is occurring for the new AEDs (eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, piracetam, pregabalin, retigabine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide). The aim of the present paper is to provide an overview of the indications for AED TDM in children. Practical issues such as choice of sample type, sample collection and processing and the concept of the reference range are discussed.

Key words: antiepileptic drugs, therapeutic drug monitoring, pharmacokinetics, drug-drug interactions, saliva

Introduction

Since 1989 there has been 18 new antiepileptic drugs (AEDs) introduced into clinical practice. There are now 27 licensed AEDs (Table 1) making these drugs among the most common medications for which therapeutic drug monitoring (TDM) is performed (Patsalos et al., 2008). Because AEDs have characteristics such as a low therapeutic index, undergo metabolism via common hepatic enzyme systems which are highly inducible and readily inhibited, exhibit non-linear pharmacokinetics and many are associated with pharmacologically active metabolites, TDM provides a pragmatic approach to their use and thus epilepsy care. That AED TDM has become so widespread can be attributed to: 1) Plasma AED concentrations correlate much better than dose with the clinical effects; 2) Assessment of therapeutic response on clinical grounds alone is difficult in most cases because AED treatment is prophylactic and seizures occur at irregular intervals. 3) it is not always easy to recognize signs of toxicity purely on clinical grounds; 4) AEDs are subject to substantial pharmacokinetic variability and thus large differences in dosage are required in different patients; and 5) there are no laboratory markers for clinical efficacy or toxicity of AEDs.

Ideally AED treatment entails achieving complete seizure freedom without significant adverse effects, but for many patients achieving optimum seizure control with minimal adverse effects is the best compromise. The aim of this review is to provide an overview of the indications for AED TDM in children.

Children – general considerations

Age markedly influences AED pharmacokinetics and plasma clearance of AEDs in children is significantly higher than adults (Perucca, 2006; Hadjiloizou & Bourgeois, 2007; Italiano & Perucca). Consequently, a child may need a 2-3 times greater weight for weight dose than that required to achieve the same plasma drug concentration in an adult. Furthermore, clearance decreases gradually throughout childhood, but the precise time course of this process is not well established and is characterized by pronounced

inter-individual variability (Perucca, 2006). Consequently, dose requirements for children are less predictable than for adults and are constantly changing, therefore TDM is particularly helpful for optimal management of this patient group (Hadjiloizou & Bourgeois, 2007; Walson, 1994).

Indications for TDM of AEDs in Children

The main indications for AED TDM are summarized in Table 2 and below we discuss these in detail. Whilst some indications may not apply to all AEDs, some indications such as identifying non-compliance and suspected drug-related toxicity and guiding management of AEDs with non-linear pharmacokinetics, apply to all AEDs.

Dose optimization on the initially prescribed AED

Plasma concentration measurement of the initially prescribed AED is particularly valuable when the best therapeutic response has been achieved in an individual and maintained for a sufficient period of time to be confident that dosage has been optimized Determination of the plasma AED concentration at a standardized sampling time will identify the “individual therapeutic concentration”, which is a useful point of reference to guide treatment if a change in response occurs requiring further follow-up (Patsalos et al., 2008). A major advantage of the “individual therapeutic concentration” approach is that it does not rely on fixed “reference ranges” and can be applied to all AEDs regardless of whether or not “reference ranges” have been clearly defined. In order to establish an individual’s therapeutic concentration, two separate determinations should be undertaken 2 to 4 months apart in order to estimate the extent of any variability (Patsalos et al., 2008).

Uncontrolled seizures

Knowledge of the “individual therapeutic concentration” will improve the management of patients who develop breakthrough seizures after a prolonged period of seizure control. For example, after a breakthrough seizure occurs, if the plasma concentration is much lower than the previously determined individual therapeutic concentration it suggests

either suboptimal compliance or a clinically important change in AED pharmacokinetics (Specht et al., 2003; Mucklow & Dollery 1978; Eadie, 1997). In a setting where seizures persist despite an apparently adequate dosage of an appropriate AED, TDM is useful to identify potential causes of therapeutic failure which may result from poor compliance (typically characterized by variable plasma concentrations, which increase following supervised drug intake) or from poor drug absorption, fast metabolism or drug-drug interactions (typically characterized by low plasma AED concentrations).

Suspected toxicity

One of the most frequent reasons why AED measurements are requested is to investigate suspected toxicity and the most common adverse effects are CNS-related and include sedation, dizziness, confusion, drowsiness, tremor and nystagmus (Patsalos & Bourgeois, 2014). The determination of all prescribed AEDs may help to identify which drug(s), if any, are contributing to suspected CNS toxicity.

Co-morbidities

The absorption, distribution, elimination and protein binding of various AEDs can be affected by various co-morbidities (co-pathologies). For example, hepatic or renal impairment, infections, burns, HIV infection and other conditions (Aronsen et al., 1972; Bowdle et al. 1980; Martyn et al., 1984; Burger et al., 1994). In addition to the alterations caused by the pathological state *per se*, drugs used to treat these conditions can cause drug-drug pharmacokinetic interactions and consequent changes in AED concentrations which can be monitored by TDM.

Whenever a concurrent condition is known or suspected to alter AED protein binding e.g. renal failure and after dialysis or surgery, when hypoalbuminemia occurs, or when patients receive drugs that compete for protein binding sites e.g. aspirin, naproxen, tolbutamide, phenylbutazone (Perucca, 1984), measurement of the free drug concentration is essential, particularly for extensively bound AEDs.

Hepatic disease can significantly alter the clearance of AEDs that are metabolized in the liver (Asconape & Penry, 1982). Furthermore, since the liver is the source of many proteins, plasma protein binding may also be affected in patients with liver disease. Since it is impossible to predict the extent of change in AED clearance in hepatic disease (Asconape & Penry, 1982) TDM (with free concentrations for highly bound drugs) is considered best practice in this patient group.

Drug-drug pharmacokinetic interactions

Polytherapy AEDs is common in children with refractory epilepsy and it is usual for children with catastrophic syndromic epilepsies, such as Dravet syndrome and Lenox-Gastaut syndrome, to be prescribed 3, 4 or even 5 AEDs in order to control seizures (Patsalos et al., 2002; Patsalos & Perucca, 2003a, 2003b). In addition, for those children that develop co-morbidities, it is inevitable that they will be prescribed non-epilepsy drugs to treat co-morbidities. In these settings the propensity of drug-drug pharmacokinetic interactions is high and can result in either an increase or a decrease in plasma AED concentrations (Patsalos et al., 2003b). Thus, if patients exhibit signs of toxicity or experience breakthrough seizures, AED TDM can help ascertain which drug is responsible for the change in clinical status and also help guide dosage adjustments so as to compensate for the interaction (Patsalos & Perucca, 2003a, 2003b). Best practice is to avoid interacting drugs (Patsalos, 2013), but if this is not possible, it is advisable to measure baseline concentrations of on-going therapy prior to making the addition.

Practical issues

Appropriate interpretation of TDM data is dependent on some practical issues such as choice of sample type, sample collection time and sample processing. Ability to use the reference range to individualize treatment is essential.

Reference range

The concept of the reference range is particularly important and regrettably it is much misunderstood. It should be remembered that the reference range is not a

therapeutic range; instead it is defined as a range of drug concentrations which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur. The reference range is based on population data derived from TDM research or from clinical drug trials of adult patients. Specific reference ranges for children are not available; instead those quoted for adults are used and this has proven useful. Because of large inter-individual differences in type of epilepsy and severity of seizures, the effective AED concentration can vary significantly from patient to patient. Consequently, patients can achieve therapeutic benefit at plasma concentrations outside these ranges and it is not unusual for some patients to have optimum seizure control at plasma concentrations below the lower value of the reference range whilst others may require (and tolerate) drug concentrations above the upper limit of the reference range (Patsalos et. al., 2008; Johannessen et al., 2003). It should be emphasized that it is important to treat the patient and not the blood concentration (Woo et al., 1988).

Sample type

AED TDM is normally undertaken in either plasma or serum and concentrations in each are similar. Saliva AED monitoring is increasingly being used (Patsalos & Berry, 2013) because of its many advantages which include:- 1) concentrations reflect the non-protein bound, pharmacologically active component in plasma; 2) saliva is easier to collect than blood and many patients prefer saliva sampling and; 3) the standard analytical methods can normally be adapted to accept saliva specimens. Since there is a greater need to monitor AED concentrations in children, there have been many studies of salivary TDM in children (Lifshitz et al., 1990; Mucklow et al., 1981; Cai et al., 1993). Overall, for children, saliva is considered more acceptable and preferred to blood sampling.

Sample collection

It is essential to collect an appropriate specimen and submit it to the laboratory together with a request form containing all the required information to allow proper interpretation of analytical findings. Since a considerable number of AEDs are currently available which have similar adverse (and beneficial) effects; and multidrug therapy is frequently necessary (particularly for refractory patients), it is recommended that the specimen be submitted to a laboratory which can provide complete analytical coverage and undertake a multidrug analysis.

Sampling time is very important. Unless toxicity is suspected, trough concentrations provide the most useful information, and samples should be collected just before the next scheduled dose and preferably in the morning after an overnight fast. Properly timed sampling should be collected at steady-state when drug absorption and distribution are completed. Samples drawn before steady-state is achieved will result in lower than predicted drug concentrations, which may prompt higher than necessary dosage adjustments. For AEDs with long half-lives (e.g. ethosuximide, phenobarbital, phenytoin, perampanel, zonisamide) the fluctuation in plasma drug concentration during a dosing interval is negligible, and samples can be collected at any time, but for the majority of AED which have shorter half-lives (e.g. carbamazepine, levetiracetam, lamotrigine, lacosamide, topiramate) it is important to standardize sampling time in relation to dose.

Summary

AED TDM is now a well-established tool for the management of epilepsy and it is of particular value in managing children with epilepsy who's metabolic and renal clearances are continually changing through to adulthood. While drug measurements are mostly undertaken in plasma many AEDs can be readily monitored in saliva. Saliva has the advantage of reflecting the free, non-protein bound, pharmacologically active concentration of drug in plasma. The reference

range is a useful population based concept, however, determination and application of the “individual therapeutic concentration” has many advantages in that it is specific for an individual whereby seizure freedom with good tolerability or optimum seizure control with minimal adverse effects is achieved.

Acknowledgement and disclosure

This article was prepared at the invitation of the Editor of the Journal of Pediatric Pharmacy.

The work undertaken by Professor P N Patsalos was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. Professor Patsalos has no conflict of interests to declare with regards to this publication.

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Table 1: Introduction of antiepileptic drugs in the United Kingdom and their current reference range.

Drug	Year of Introduction	Plasma reference range[a]	
		mg/L	µmol/L
Phenobarbital	1912	10-40	43-172
Phenytoin	1938	10-20	40-79
Primidone	1952	5-10 [b]	23-46 [b]
Ethosuximide	1960	40-100	283-708
Carbamazepine	1963	4-12 up to 2.3[c]	17-51 up to 9.1[c]
Diazepam	1973	NE[d]	NE[d]
Valproate	1974	50-100	346-693
Clonazepam	1974	0.02-0.07	0.06-0.22
Clobazam	1982	0.03-0.3 0.3-3.0[e]	0.1-1.0 1.0-10.5[e]
Vigabatrin	1989	0.8-36	6-279
Lamotrigine	1991	2.5-15	10-59
Gabapentin	1993	2-20	12-117
Felbamate	1993	30-60	126-252
Topiramate	1995	5-20	15-59
Fosphenytoin	1996	10-20[f]	40-79[f]
Piracetam	1997	NE[d]	NE[d]
Tiagabine	1998	0.02-0.2	0.05-0.53
Oxcarbazepine	2000	3-35 [g]	12-139 [g]
Levetiracetam	2000	12-46	70-270
Pregabalin	2004	2-8	13-50
Zonisamide	2005	10-40	47-188
Rufinamide	2007	30-40	126-168
Stiripentol	2007	4-22	17-94
Lacosamide	2008	2.5-15	10-59
Eslicarbazepine acetate	2009	3-35 [h]	12-139 [h]
Retigabine	2011	NE[d]	NE[d]
Perampanel	2012	0.18-0.98	0.50-2.74

a = for clarity values can be rounded up or down by laboratory; b = during treatment with primidone both primidone and the pharmacologically active metabolite phenobarbital should be monitored; c = refers to values for the pharmacologically active metabolite carbamazepine-epoxide; d = not established; e = refers to values for the pharmacologically active metabolite N-desmethyl-clobazam; f = based on values for phenytoin; g = all values refer to the active metabolite 10-hydroxycarbazepine; h = the reference range is that quoted for the active metabolite of oxcarbazepine namely10-hydroxycarbazepine because the two molecules are identical

Table 2: Indications for antiepileptic drug (AED) therapeutic drug monitoring in children.		
	Indication	Comment
1	After initialization of AED treatment or after dose adjustment.	A preselected reference range can be targeted for the individual patient.
2	Upon achievement of optimum desired clinical response.	This allows for the "individual therapeutic range" to be established.
3	To determine the magnitude of a dose change.	This is particularly important for AEDs that show dose-dependent pharmacokinetics (e.g. phenytoin, carbamazepine, valproate, gabapentin, stiripentol and rufinamide).
4	When toxicity is difficult to assess clinically.	Concentration-related AED toxicity is more readily identified and is particularly helpful when young children with mental disability are being evaluated.
5	When seizures persist despite the prescribing of an adequate/typical dosage.	Occurs with a fast metabolizer or a patient that is non-complying with their AED medication.
6	When pharmacokinetic variability is expected.	This category includes children and during hepatic disease, renal disease, various pathologies, post-surgery and drug-drug pharmacokinetic interactions.
7	The clinical response has unexpectantly changed	The cause of the change could be readily identified as it could be the consequence of many reasons.
8	Suspected non-compliance	Recent non-compliance can be readily identified. However, long-term compliance or variable compliance cannot be identified.