Review Article

Therapeutic Drug Monitoring of Antiepileptic Drugs: Indications and Modalities

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1. Introduction

Epilepsy is a neurological disease that affects over 50 million people worldwide [1-5]. Treatment is primarily medical. Since 1990, in addition to conventional antiepileptic drugs, 16 new drugs have been accessible to patients [6-9]. In general; side effects of antiepileptic drugs represent one of the most important causes of treatment failures of epilepsy [10-12]. One tool that physicians can use to decrease and manage this disease is the Therapeutic Drug Monitoring (TDM) of these drugs. In addition to assistance in managing side effects, TDM will also guide the physician in assessing non-compliance, changes in the pharmacokinetics that may occur between individuals and the study of factors that are responsible for these variations [13-19]. Through a literature review, it will identify the clinical situations for which TDM is required, the role of this tool in managing epilepsy and how to use it. We did a literature search in 2 databases, PUBMED and MEDLINE (1980 to 2014) with the following keywords "epilepsy" "antiepileptic drugs" and "therapeutic drug monitoring" combined to "management of epilepsy."

2. Indications of Therapeutic Drug Monitoring of Antiepileptic Drugs

TDM of antiepileptic drugs is a valuable aid to the clinicians in the management of epilepsy, but its use should not be systematic. A week audit was performed by Sharpe, et al. [20], at the University Hospital in Belfast on the nature of clinical situations in which TDM had been accomplished. The results showed that almost 50% of TDM requests had no satisfactory clinical reason. This fact is consistent with the results of Jannuzzi, et al. [21]. These authors conducted a study in 180 epileptic patients who were combining two or three of these drugs: carbamazepine (CBZ),

phenytoin (PHT), valproic acid (VPA), phenobarbital (PB) or primidone (PRM). The patients were divided into 2 groups. For the first group, the dose taken was based on the level of the prescribed antiepileptic drug, while for the second group the doses were adjusted according to clinical criteria. The results showed no significant difference in the individualization of doses between the 2 groups and frequency of adverse events was almost identical for both groups. Thus the request for TDM should not be systematic and it must be limited to the listed specific indications:

2.1 Dose adjustment

Dose adjustment is the first strategy that physicians adopt to control the patient's therapy [22]. With TDM, clinicians can have an idea on the safety margin of the drug taken as to avoid the occurrence of adverse effects. Mathew et al. [23] have illustrated it in a group of 69 children where levetiracetam TDM had played a very important role in non-responders to treatment. Once the dose is adjusted, the clinician will know the effective plasma concentration to the patient and will use it as a reference when making decisions if there are changes in the clinical status over time. Dosages are done when concentrations are steady and this state is obtained after a time equal to 7 half-lives after the first drug administration [24-28].

2.2 Ineffective therapy

This may be due to poor compliance despite adequate doses. Indeed, adolescents and young adults are a subgroup with a higher risk for non-adherence [29-30]. The results of the study of Specht, et al. [31] have shown that 44% of their 52 patients had plasma concentrations more than 50% below the reference concentration. The non-compliance of these patients was the cause of their low plasma concentrations. The ineffectiveness of treatment may also be due to drug-resistant epilepsy. TDM can then guide the clinician to a change of the prescribed antiepileptic drug since the plasma levels are usually in the therapeutic range but without any clinical improvement.

2.3 Toxicity

The patient may develop signs or symptoms of poisoning. TDM will show if the antiepileptic drug is the cause of the toxicity, especially in patients whose status is difficult to assess clinically as young children and subjects with mental disorders.

2.4 Change in pharmacokinetics

2.4.1 Changes in metabolism and elimination of antiepileptic drugs: it will review mainly those related to drug interactions, age and gender:

- Drug interactions can change the hepatic metabolism. The most important are those implying the isoenzymes of the cytochrome P450. These interactions can occur with antiepileptic drugs in case of combination therapy [18, 28, 32-38]. Surely, with the aim of showing the effect of the concomitant administration of one or several antiepileptic drugs on the concentrations of the carbamazepine, Fukuoka et al. [39] released a study of 119 epileptic patients with carbamazepine only, 91 patients with carbamazepine and either phenobarbital or phenytoin and 64 patients with all the 3 antiepileptic drugs. Using a multiple regression analysis, these authors showed that phenobarbital decreases the concentration of carbamazepine

by a factor of 0.77 while with phenytoin this decrease factor is 0.71. Other interactions can occur between antiepileptic drugs and other classes of medicines [9, 40-41]. Christensen, et al. [42] conducted a study on the effect of the oral contraceptive drugs on the lamotrigine steady state plasmatic concentrations. They showed that after stopping oral contraceptive drugs, the lamotrigine plasmatic concentrations almost doubled. This proves the inductive effect of these products on the metabolism of this antiepileptic drug. The same results were found by Galimberti et al. [43] on the plasmatic concentrations of the free and total fractions of valproic acid when taken with ethinylestradiol.

- With age, metabolic and elimination changes occur both in children and in the elderly [23, 44-46]. To show the importance of the dosage of antiepileptic drugs in children, Battino, et al. [33] compared the clearance of topiramate in a group of 70 children aged between 1 and 17 years to an adult group of 140 patients aged between 18 and 65 years. Their results showed that the clearance of topiramate was 42% higher in children than in adults. Another study was performed in a group of elderly patients with epilepsy aged over 65 years by Battino, et al. [47]. These patients were taking carbamazepine, TDM results of this drug at steady state showed a 23% decrease in clearance of carbamazepine as compared to the control group whose age was between 20 and 50 years.

- Gender-related changes: Sirmagul, et al. (18° conducted a study in over 8000 epileptic patients and it showed a gender effect on the plasma concentrations of carbamazepine, phenytoin and valproic acid. Carbamazepine plasma concentrations were higher in men while those of phenytoin and valproic acid were higher in women. This study concluded that CYP2C9 and CYP2C19 responsible for the metabolism of phenytoin and valproic acid are more active in men than women and CYP3A4, responsible for carbamazepine metabolism, are more active in women than men.

2.4.2 In case of changes in distribution: During pregnancy, physiological changes may impact mainly on the distribution of antiepileptic drugs between the mother and the foetus as well as the elimination of antiepileptics [34, 48]. A study was done in a group of 63 epileptic women during childbirth [49]. These patients were taking either lamotrigine alone or in combination with carbamazepine or valproic acid. Blood samples were taken from the mothers and the umbilical cords. The results of this study showed that in case of monotherapy, the umbilical cord/mother concentration ratio was between 0.40 and 1.38, thus showing the degree of passage of lamotrigine from the mother to the foetus. Co-administration of valproic acid led to a significant increase in the lamotrigine concentrations of both the mother and the umbilical cord samples with a significant 65% decrease in the clearance of lamotrigine. With carbamazepine, increased clearance of lamotrigine was not significant, but concentrations of valproic acid and carbamazepine in the umbilical cord were respectively 30% higher and 20% lower than those in the mothers' samples.

2.4.3 Changes in plasma protein binding: In addition to pregnancy, age, some liver or kidney diseases and other medical conditions can be associated with hypoalbuminemia which results in a change in the concentration of the free fraction of antiepileptic drugs [14, 16, 34, 50-56]. However, in the management of epilepsy, the measurement of

total serum concentrations is sufficient for TDM and the majority of analytical methods do not discriminate between the free fraction of antiepileptic drug and the one bound to serum proteins. So if the free fraction increases, the measurement of total serum concentration will underestimate the amount of the free fraction and in these case signs of toxicity might be observed. This was reported by Chan, et al. [57] about an epileptic patient taking valproic acid, phenytoin and carbamazepine who presented vomiting, ataxia and bilateral horizontal nystagmus. The dosage of these 3 drugs showed normal values, but the free fractions of each drug showed a high concentration of valproic acid. A reduction in the dose of this antiepileptic drug led to the disappearance of the toxicity symptoms. In addition, the results of Hong et al. [58] showed that the serum levels of free phenytoin in patients with low rate of serum albumin were 20% higher than in patients with normal rates of albumin serum.

2.4.4 Pharmacokinetic changes related to genetic polymorphism: Currently, an increasing number of studies demonstrate that the inter-individual variability associated with response to antiepileptic drugs can be attributed to genetic polymorphism [59]. Taur, et al. [60] conducted a study in 115 patients treated with phenytoin alone or in combination with phenobarbital or carbamazepine or all three together. In these patients, they showed that the activity of P-glycoprotein was higher in the non-responders to antiepileptic treatment (n= 68) when compared to the responders (n=47). They have concluded that the response to antiepileptic treatment appears to be modulated by the polymorphism of the efflux transporter which has the consequence of reducing their bioavailability and limit their access to the brain. Another study [61] of 425 patients taking carbamazepine and 281 other under phenytoin, showed the existence of a significant association between the polymorphism of the SCN1A gene and regular use of maximal doses of carbamazepine and phenytoin to control seizures. Recently, the FDA has issued a warning about the genetic tests that must be performed in epileptic Asian people to predict severe skin reactions to carbamazepine [62].

2.4.5 Problems caused by non-linear pharmacokinetics, as is the case of phenytoin [18, 24, 30, 50, 58, and 63]: Shakya, et al. [30] conducted a study in 382 epileptic patients who were taking carbamazepine, valproic acid or phenytoin as monotherapy or in combination therapy with 2 or 3 antiepileptic drugs. Blood levels showed that 35.8% of the patients who were under phenytoin had therapeutic concentrations and the others had subtherapeutic or toxic rates. For carbamazepine and valproic acid, this percentage was 79.3% and 62% respectively. So because of its saturable kinetic, monitoring plasma concentrations of phenytoin is necessary.

2.5 Drug formulation-Change

Substitution of a formulation by another one should be well monitored by the treating physician. Epilepsy is a special disease because of its specificities, the low therapeutic margin of some antiepileptic drugs, the need to individualize therapy to control crisis, and the negative consequences of uncontrolled epilepsy. Consequently, a substitution should be considered with a lot of care [64].

2.6 In Case of substitution of a princeps to a generic drug

The use of generic drugs in epilepsy stirred a lot of controversies, because of the fear that this substitution might be accompanied by some side effects with possible variations in plasma concentrations of the drug. Several

recommendations were issued for this purpose, including the patient's consent, careful monitoring of the patient's clinical status and evolution in plasma of the newly prescribed generic drug [64-65].

3. Modalities of TDM

3.1 Sampling time

When to draw blood samples is the crucial phase of therapeutic monitoring for all drugs since the correct interpretation of obtained blood concentrations is dependent on sampling time. Sampling time is based on many parameters such as the half-life of the drug, its resorption phase length and/or distribution phase, bioavailability, route of administration (oral, intramuscular, intravenous), pharmaceutical formulation and frequency of intake. A sample drawn at the wrong time will give either a higher or lower concentration than expected and will distort the dose adjustment by the clinician, leading to a risk of inefficiency or toxicity. Since most anticonvulsants are administered orally, blood samples should be obtained at steady state reached after 7 half-lives of the drug and just before the new administration.

3.2 Matrix of sample

Serum or plasma represents the matrix of choice for TDM. Through current technology, research is directed into the development of new non-invasive analytical matrices, such as saliva, which offers an advantage especially in children [66].

3.3 Dosing Methods

The availability of a simple analytical method that is accurate, reproducible and inexpensive is essential to the good use TDM. Several analytical techniques are used for the determination of antiepileptic serum concentrations. Most of the time, it is the high performance liquid chromatography (HPLC) or immunological methods [66-71]. With the increasing number of new antiepileptic drugs on the market, therapeutic monitoring was guided by the development of new efficient methods such as liquid or gas chromatography-mass spectrometry [72-75].

3.4 Interpretation results

For the results of TDM to be useful and helpful for the clinicians in making their decisions, the interpretation of plasma concentrations should allow some flexibly and the pharmacologist should not be looking only if the concentrations ranges are within the therapeutic range. The reference values of the therapeutic range are only statistical ones, and they cannot be applicable to all patients. There are patients who can present an optimal effect at higher concentrations than the reference values and others who will have toxic effects within this range. In addition to serum concentrations, the interpretation must also consider the patient's clinical status, age, sex, the pharmacokinetic characteristics of the molecule, the associated therapy, the time between the last dose and sampling and genetic polymorphism [14, 16, 24, 59]. In children, the results should be interpreted considering weight, height and body surface area of children, in addition to the parameters already mentioned. Indeed, in their interpretation of the concentrations of the free fraction of valproic acid, Ueshima and colleagues [56] during their study of 30

children with epilepsy taking valproic acid did consider all these factors which helped them correlate between the clinical status of the children and their plasma values.

4. Conclusion

Monitoring plasma concentrations of antiepileptic drugs have become a reasoned act that is limited to very specific clinical indications. The challenge is to undertake randomized studies on the positive impact of TDM on clinical outcomes in order to show that this approach has a role in the long-term seizure control and the improved quality of epileptic patients' life.

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