Therapeutic Drug Monitoring of Antiepileptic Drugs in the 21st Century

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Summary

Therapeutic drug monitoring (TDM) is only useful if certain criteria are fulfilled and its limitations are known. Ideal candidate drugs are those with significant inter-individual pharmacokinetic (PK) variability, low intra-individual PK variability and a good correlation between blood level and clinical response or side effects. Although the clinical contribution of TDM for some older antiepileptic drugs (AEDs) is well established (phenytoin, valproic acid, carbamazepine, phenobarbital), its relevance for the newer AEDs is hardly documented, in part because their PK characteristics make them questionable TDM candidates. Nevertheless, a majority of them could theoretically benefit from monitoring under specific situations. We summarize here the strategies proposed regarding TDM for currently available AEDs. Future developments include AEDs measurement in saliva, sharper tailoring of TDM (individual therapeutic intervals), availability of point of care TDM tools, and randomized controlled TDM trials for the newer AEDs.

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Key words: TDM, AEDs, therapeutic management, pharmacokinetics

Therapeutisches Monitoring der Antiepileptika im 21. Jahrhundert

Die Serumspiegelbestimmung von Medikamenten ist nur sinnvoll, wenn bestimmte Kriterien und Grenzen bekannt sind. Ideale Kandidaten sollten eine signifikante inter-individuelle, aber eine bescheidene intra-individuelle Variabilität und eine gute Korrelation zwischen Spiegeln und biologischer Antwort aufweisen. Obwohl die Serumspiegelbestimmung für ältere Antiepileptika (Phenytoin, Phenobarbital, Vaproat, Carbamazepin) seit langer Zeit breit anerkannt ist, ist die Indikation bezüglich neue Antiepileptika bisher nicht klar bewiesen, dies auch in Hinsicht auf ihre pharmakokinetischen Charakteristika. Nichts desto trotz könnte die Serumkonzentrationsbestimmung theoretisch der Mehrheit der neuen Antiepileptika dienen, zumindest in spezifischen klinischen Lagen. Hier werden die Ansätze vorgestellt, welche für ein Monitoring der Antiepileptika vorgeschlagen werden. Weitere mögliche Entwicklungen sind Speichelanalysen, die Individualisation der therapeutischen Referenzen, die Verfügbarkeit von Automaten in der Nähe der Patienten, als auch randomisierte kontrollierte Studien, um die neuesten Substanzen besser zu erfassen.

Schlüsselwörter: Therapeutisches Monitoring, Antiepileptika, therapeutisches Management, Pharmakokinetik

„Monitoring thérapeutique" des médicaments antiépileptiques au 21ème siècle

Le suivi pharmacologique ou « monitoring thérapeutique des médicaments » est utile si certains critères sont remplis et ses limites connues. Les médicaments candidats idéaux présentent une variabilité pharmacocinétique interindividuelle significative, une faible variabilité intraindividuelle, et une bonne corrélation entre les concentrations sanguines et la réponse clinique ou les effets secondaires. Bien que la contribution clinique du monitoring pour certains anciens antiépileptiques soit établie (phénytoïne, acide valproïque, carbamazépine, phénobarbital), sa pertinence pour les médicaments plus récents est clairement moins bien documentée, entre autres parce que leurs caractéristiques cinétiques ne les désignent pas comme de bons candidats. Néanmoins, une majorité d'entre eux pourraient théoriquement bénéficier d'un suivi des concentrations dans certaines situations spécifiques. Nous ré-

sumons ici les stratégies proposées concernant le suivi thérapeutique individuel des antiépileptiques actuels. Parmi les évolutions souhaitables figurent le dosage des médicaments dans la salive, une individualisation des concentrations cibles (intervalles thérapeutiques individuels), la disponibilité d'outils de monitoring sur le lieu de soin, et des essais cliniques contrôlés pour le monitoring des antiépileptiques les plus récents.

Monitoring terapeutico dei medicamenti antiepilettici nel 21. secolo

Il controllo farmacologico o "monitoraggio terapeutico dei medicamenti" è utile unicamente se criteri ben determinati e i relativi limiti sono conosciuti. I medicamenti candidati ideali si distinguono per una significativa variabilità farmacocinetica interindivuale, una limitata variabilità intraindividuale, e una correlazione ragionevole tra le concentrazioni sanguigne e la risposta clinica o gli effetti secondari. Se la contribuzione clinica del monitoraggio terapeutico per la maggiorparte dei medicamenti "classici" (fenitoina, valproato, carbamazepina, fenobarbital) è chiaramente riconosciuta da tempo, il ruolo relativo alle sostanze più recenti è molto meno documentato, anche a causa delle loro caratteristiche cinetiche. Ciò nonostante, la maggioranza dei nuovi antiepilettici potrebbe teoricamente beneficiare d'un monitoraggio delle concentrazioni, soprattuto in situazioni particolari. Si riassumono in questo contributo le strategie proposte in questo senso, e tra le evoluzioni all'orizzonte si menzioneranno il dosaggio salivario, un'individualizzazione delle concentrazioni ottimali, e lo sviluppo di macchine di misura portatili che permettano un utilizzo in prossimità del paziente. Infine, è importante sottolineare il bisogno di studi prospettici in questo ambito.

When can drug levels be useful to measure?

The concept of therapeutic drug monitoring (TDM) in blood, and potentially in other biological matrices, is led by the assumption that the pharmacodynamic effects of some drugs correlate better with circulating concentrations than with administered doses. TDM encompasses both drug quantification in a sample and pharmacological interpretation for dosage adjustment.

Measurement requests for antiepileptic drugs (AEDs) and interpretation of the results are usually made by the prescribing physician. His challenges are both to decide appropriately on sampling, and to adjust drug dosage in consequence. Development of high performance analytic technologies now gives potential access to quantification of a large number of drugs. Yet not all are good candidates for TDM. Drugs of choice to allow for reliable monitoring are those that display large inter-individual and low intra-individual pharmacokinetic (PK) variability, and good correlation between blood concentrations and the clinical response or side effects [1].

In defining TDM strategies, three situations can be distinguished. There can be either an indication for systematic TDM on a regular basis, or a need for initial adjustment up to finding the right dose, or solely an indication for "on-need" control when confronted with clinical issues such as treatment resistance, side effects, or drug interactions. In the case of AEDs, systematic TDM is not usually advised, while the two later strategies are more widely used in epilepsy management. Initial adjustment measures are mostly requested in acute situations (emergency settings and after a loading dose), whereas TDM use in chronic follow-up of patients with epilepsy is mostly resorted to on an "on-need" basis. A drug level should only be requested if the result is expected to contribute to the patient's management in answering a specific question, such as "is my patient having seizures despite circulating drug exposure within the generally acknowledged therapeutic interval? If not, how to modify the dosing regimen? Or should the patient be prescribed another drug?", "will this measure help answer doubts about compliance?", "will it help to support or refute clinically suspected toxicity?".

What are the potential pitfalls in drug level interpretation?

Some of these specific questions raised by the physician hoping for a contribution of the drug level in the therapeutic decision may be poorly answered, or the level erroneously interpreted, if potential limitations are not considered. Concentration-effect data and intra-individual variability are often lacking in the early post-marketing years of a drug, leaving the question of the value of TDM unanswered. Exploratory TDM can be deemed of interest in some "on-need" situations, but the reference concentration interval must be considered as tentative, as opposed to a validated therapeutic interval based on available concentration-effect (PK-PD) data for a given indication. A blood level may not help predict future levels with or without dosage modification if the intra-individual variability is significant. The time or mode of blood sampling may lead to biases. For a blood concentration to be representative of exposure at a given dose regimen, it must be sampled ideally just prior to the next dose (trough level), or at least after the distribution phase. There also must be enough time given to reach the steady state, so that no further accumulation (or decrease resulting from auto-induction or following a dosage reduction) is expected.

Depending on the drug, steady state may be reached only after several days to weeks following treatment initiation, dosage modification, or introduction/interruption of an interacting drug. Co-medications should be known when interpreting a drug level, as well as the stage of a possible ongoing pregnancy. Other aspects also of importance, but usually of less concern in outpatient practice, are accurate dose calculation (intravenous administrations), physico-chemical compatibility with nutrients or drugs given through the same line, sampling route (risk for dilution or contamination), and the possible need to correct a total concentration level for dysproteinaemia.

Classical antiepileptic agents: the "good old TDM"

AEDs are historically represented in TDM for a fair number of reasons, notably the complexity and heterogeneity of epilepsy, the lack of biological markers or specific clinical signs aside from frequency of seizures to assess treatment efficacy or toxicity, and the complex pharmacokinetics of early drugs [2].

Yet AEDs aren't a homogenous therapeutic class. **Table 1** [3-20] displays those currently available in Switzerland, according to generation of marketing, with their mean PK characteristics, peculiarities, suggested sampling timeline, reference interval and our estimate of the level of evidence for TDM usefulness.

TDM of first and second generation AEDs will not be discussed in detail. Those of interest for TDM remain phenytoin, valproic acid, carbamazepine and phenobarbital, as they are yet prescribed and their reference interval is defined (narrow interval in particular for phenytoin). Their high inter-individual variability can be explained by a hepatic metabolism mediated by cytochromes P450, subject to genetic polymorphism (non-functional CYP 2C8/9 or 2C19 allelic variants with consequently high blood levels at conventional dosages), and to a significant potential for drug interactions (CYP 2C8/9, 2C19, 3A4, 2E1). Enzyme auto-induction can also contribute to this variability (carbamazepine, phenobarbital, phenytoin), as well as saturable metabolism (phenytoin, valproic acid). Furthermore, if highly protein bound drugs with low hepatic extraction (mostly phenytoin and valproic acid) are given to a patient presenting hypoproteinaemia, a low total drug concentration may falsely encourage the clinician to increase the dose, while the free (biologically active) drug concentration is in fact already in the target range. Quantification of free phenytoin or free valproic acid concentrations may therefore prove useful, on a case to case basis, when a significant discrepancy between the total and free serum concentrations is suspected [21-22]. Eventually, metabolites of AEDs can contribute to toxic effects, such as is the case of neurotoxicity caused by epoxy-10-11 carbamazepine.

Only one randomized controlled trial on TDM usefulness for AEDs could be identified [23-24], which failed to show a significant benefit of TDM over therapeutic decisions without drug monitoring, based on seizure control at 12 months. But this study had several limitations (small number of patients, inclusion restricted to patients naïve from previous AED therapy with indication to initiate monotherapy). The lack of robust randomized controlled studies for classical AEDs TDM is mainly explained by historical problems, and does not jeopardize our appreciation that TDM remains useful for initial dose-finding in phenytoin and phenobarbital therapy, especially in ICU or -emergency settings, while it should be used on a more "on-need" basis in answer to a clinical question (poor control, suspected adverse effect) in valproic acid or carbamazepine use.

Should TDM be generalized to the more recent generation of antiepileptic drugs?

Few sources address third generation AEDs TDM and its relevance. Only one group has estimated TDM usefulness for these drugs, which they considered to range between "possibly useful", "remains to evaluate" or "not useful", based on very limited data (French Society of Pharmacology and Therapeutic (FSPT)).

Some of the third generation AEDs show significant interindividual PK variability, in part due to metabolic interactions or polymorphisms as they are hepatic cytochrome or glucuronidase substrates (**Table 1**). These drugs appear of theoretical interest for TDM: lamotrigine, lacosamide, zonisamide, felbamate, and possibly perampanel and retigabine. However, aside from felbamate [25] and lamotrigine [26-27], a clear correlation between blood level and clinical response or side effects has not yet been demonstrated for these drugs. To our best knowledge, TDM of perampanel and retigabine were never explored to this date.

Other third generation drugs are hypothesized to show low inter-individual variability, or more easily predictable variability, as they are almost exclusively eliminated unchanged through the kidney in proportion to renal function (gabapentin, pregabalin and levetiracetam) or metabolized by cytochrome- or glucuronidase-independent pathways (**Table 1**). Although expected of limited interest for TDM, some may show unexpected higher interindividual PK variability, and "on-need" monitoring may be of use in specific situations such as in children or during pregnancy [28-29]. This explains some discrepancies between available pharmacological characteristics and estimated usefulness of TDM: in fact levetiracetam, topiramate, oxcarbazepine, rufinamide and perhaps gabapentin [30] could yet be explored as TDM candidates (current literature only reports a dose-effect relationship for rufinamide). Low interindividual PK variability has been described for topiramate, but a correlation between blood level and clinical response/ side effects has been suggested, TDM being therefore

Table 1: Main pharmacokinetics parameters, metabolism and therapeutic drug monitoring recommandations for antiepileptic drugs

| Generation | DCI | Clinical Pharmacology | | | Metabolism | | | | | | Interindividual variability in PK | TDM | | |
| | | t½ (h) | Protein Binding (%) | Renal Excretion Unchanged (%) | Cytochrome P-450 Isoenzyme Associated with Metabolism | | | UGT | Other | Active Metabolites | | Suggested sampling timeline (d) | Therapeutic Range (mg/L) | Usefulness for the treatment management |
					CYP2C8/9	CYP2C19	CYP3A4/5							
1 (1850-1959)	primidone	3-12	~10	~65						PEMA (Phenobarbital)	++	2-4	5-10	exploratory
	phenobarbital	70-140	~55	20-25	Substrate Major (auto)inducer	Substrate (auto)inducer	inducer	-	Substrate CYP2E1	No	+++	15-29	10-40	recommended
	phenytoin	Variable, ↑ with ↑ blood concentration	~90	~5	Substrate inducer	Substrate inducer	inducer	inducer	Substrate CYP2E1	No	+++	6-21	10-20 ff 1-2	recommended
	ethosuccimide	40-60	0	~20	Substrate	Substrate	Substrate Major	Substrate	Substrate CYP2B6	No	+++	8-12	(40-100)	exploratory
	clobazam	10-30*	85	<1	-	Substrate	Substrate Major	-	After CYP3A4 N-acetyltransf.	Yes	++++	2-8	(0.03-0.30)	uncertain
	clonazepam	17-56	86	<1	-	-	Substrate	-	-	No	++	4-10	0.013-0.070	uncertain
2 (1960-1979)	carbamazepine	8-20*	75	~2	Substrate inducer	inducer	Substrate (auto)inducer	-	-	Yes	+++	2-5	4-12	recommended
	valproate	12-16	~90 saturable, ↓ with ↑ concentration	1-3	Substrate inhibitor	Substrate	-	Substrate inhibitor	-	No	+++	2-4	50-100 ff 5-15	recommended
	sultiame	8-15	29	32	?	Substrate? inhibitor?	?	?	?	No	?	2-4	(2-10)	uncertain
	lacosamide	13	<30	40	?	Substrate Major	?	?	?	No	±	2-3	(10-20)	uncertain
	perampanel	66-90	~95	~2	-	-	Substrate	Substrate	-	No	++	14	?	uncertain
3 (1980-now)	felbamate	16-22	25	50	Inhibitor	Substrate inhibitor	Inducer	-	Substrate CYP2E1	No	++	3-5	(30-60)	possibly useful
	retigabine	8-10	~80	20-30	-	-	-	Substrate	-	Yes	+	2	?	uncertain
	oxcarbazepine	2*	60	~1	-	Inhibitor	inducer	inducer	Arylketone reductase	Yes	++	2-3	(3-35)	possibly useful
	rufinamide	6-10	~35	~2	-	-	Weak inducer?	-	Enzymatic Hydrolysis	No	+	1-2	(30-40)	possibly useful
	vigabatrin	5-8	0	60-80	Inducer?	Inducer?	-	-	-	No	+	2	(0.8-36)	uncertain
	topiramate	20-30	9-17	40-70	?	inhibitor	?	?	-	No	+	4-5	(5-20)	possibly useful
	gabapentin	5-9	0	~100	-	-	-	-	-	No	±	2	(2-20)	possibly useful
	pregabalin	5-7	0	~100	-	-	-	-	-	No	±	2	?	exploratory
	levetiracetam	6-8	<10	66 + Tubular Reabsorption	-	-	-	-	Enzymatic Hydrolysis	No	+	2	(12-46)	possibly useful
	zonisamide	50-70 +CA	40-60 +CA	15-30	-	Substrate	Substrate Major	-	-	No	++	10-15	10-40	possibly useful
	lamotrigine	15-35	55	10	-	-	-	Substrate (auto)inducer	-	No	++	3-7	3-15	possibly useful

Interindividual variability is quantified by the number of + (+++ for high, + for low)
Therapeutic range between brackets if there is no clear correlation between blood concentration and clinical effect
*Active metabolite with prolonged half-life

Table 2: Antiepileptic drugs for which therapeutic drug monitoring could be contemplated in saliva

Generation	DCI	Saliva monitoring	
		Free fraction	Total serum
1 (1850-1959)	phenytoin	S	C
	ethosuximide	/	S
2 (1960-1979)	clobazam Ndesmethyl-clobazam	S	S
	carbamazepine epoxide CBZ	C	C
	valproic acid	no correlation	no correlation
3 (1980-now)	lacosamide	S	?
	oxcarbazepine 10-HOcarbazepine	?	S
	topiramate	?	S

C: Correlation between blood and saliva levels ($r^2 > 0.8$)

S. Blood and saliva levels are similar (concordance > 0.8)

considered "possibly useful" in this case.

Our estimation of TDM usefulness is based on the above considerations as well as the FSPT publications. We would practically recommend "on-need" TDM for any of the third generation AEDs for which TDM is considered "possibly useful" in **Table 1**. Of note, an isolated measurement of any drug can inform about compliance (if the concentration is undetectable, especially in case of seizure recurrence) or about frank toxicity (markedly high concentration).

Do pregnant women require extra considerations when monitoring AED treatment?

Data and indication to further tailor drug monitoring in certain populations are growing, such as in pregnancy. As evidence for a low teratogenic potential of some new AEDs becomes available [31], pharmacokinetic observations suggest a need for close measurement and adjustment (dose increase) in advanced pregnancy for several of these agents as a consequence of increased renal elimination, accelerated metabolism and body fluid increase. This is notably the case for lamotrigine, for which TDM in pregnancy is part of practice parameters according to the American Academy of Neurology and the American Epilepsy Society [32]. Phenytoin, and to a lesser extent carbamazepine, as well as levetiracetam and oxcarbazepine, are likely to require a dose increase in pregnancy [33]. Scarce data on topiramate suggest that its clearance is also increased in pregnancy, but this drug should be given only in mandatory situations, as its teratogenic potential has been insufficiently studied (with conflicting results).

Do practical tools exist to help with TDM of AEDs?

Various computer applications are already available on the market to help guide in treatment adaptation, however they are not intuitive to use and expensive. There is a real need for a practical bedside tool to help ascertain reliable sampling (when and how to sample?) and level interpretation (how to modify the treatment?). Such software is being developed and should be available within the next couple of years.

Future developments

The concept of TDM is an approach to personalized medicine. But one step ahead, individualized therapeutic intervals for AED may be defined, thus refining the concept of pharmaco-sensitive or -resistant epilepsy [4]. Pharmacodynamic variability within a same type of epilepsy supports the rationale for an individual targeted interval [34]. A patient-specific, relatively narrow concentration interval could be determined based on two blood samplings performed during satisfactory control of seizures, at some distance to take the variability into consideration. Such clinically guided targets might be of particular interest for third generation AEDs, or in the context of polytherapy, where therapeutic intervals are poorly defined. For example, lower target levels have been suggested for the combination of valproic acid and lamotrigine or carbamazepine [35], as a pharmacodynamic interaction has been suggested.

Drug dosing in saliva is another development direction of AEDs TDM [36]. As it can be performed by a non-medically trained person and is less invasive and better accepted. The salivary concentration of some AEDs (**Table 2**) was shown to be proportional ("correlated") to the plasma level in about one third of available AEDs (e.g. phenytoin, carbamazepine), and in a

few cases the blood to saliva ratio nears 1, (e.g. ethosuximide, oxcarbazepine, topiramate and possibly levetiracetam). Similarity between salivary and plasma or serum free levels was documented also for phenytoin.

Conclusion

TDM of AEDs is a tricky exercise, requiring background knowledge on criteria for requesting a measure, standardized sampling times and procedures, and principles as well as potential pitfalls regarding its interpretation. TDM remains recommended for initial adjustment and "on-need" situations for phenytoin and phenobarbital, and on a mere "on-need" basis for valproic acid and carbamazepine. Although best explored for lamotrigine, TDM of the newer AEDs remains of uncertain clinical contribution. It could be of value in particular situations for at least half of these new drugs. Because the real benefit of TDM over therapeutic choice based purely on clinical follow-up remains unknown, it would be acceptable to consider randomizing patients into TDM versus no-TDM clinical trials. Further research is necessary to better define the usefulness of TDM for those increasingly prescribed drugs.

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