Anticonvulsant Therapy and the Role of Therapeutic Drug Monitoring (Part 2)

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INTRODUCTION

The success of any fixed dosing regimen most often is based on the patient's clinical response to the drug. Fixed dosing regimens are designed to generate plasma drug concentrations (PDCs) within a therapeutic range, i.e., achieve the desired effect while avoiding toxicity. However, a therapeutic range (C_{min} and C_{max}) is a population parameter that describes the range between which 95% of the animals might respond. Response below the therapeutic range does not necessarily indicate therapy is not needed; likewise, failure should not be considered only if the drug is above the maximum range. For some patients, the maximum range will need to be exceeded and should be considered if the drug is safe and response is sufficient. Thus, the absence of seizures in a dog with subtherapeutic concentrations is not justification for discontinuing the drug. On the other hand, a very small proportion of animals respond at concentrations higher than the recommended maximum; and risk–benefit considerations should determine the need to add a second drug. Therapeutic drug monitoring (TDM) is all about determining the patient's therapeutic range. Boothe*et al.* (*J Am Vet Med Assoc* 2012) have demonstrated that phenobarbital can control seizures in up to 80% of dogs when monitoring is used to guide therapy. Bromide offers reasonable efficacy at 65%.

PRINCIPLES OF THERAPEUTIC DRUG MONITORING (TDM)

Marked inter-individual variability in physiology, response to disease, and response to drugs results in variability in dose-response relationships. The most recent examples are Collie breeds with the MDR gene mutation, and drug interactions involving CYP3A4 or P-glycoprotein. Changes in drug metabolism and excretion induced by age, sex, disease, or drug interactions are among the more important factors that can cause PDC to become higher or lower than expected. TDM replaces the trial and error approach to dosing regimen designs that may prove costly both financially and to patient health. Monitoring is indicated in clinical situations in which an expected therapeutic effect of a drug has not been observed or in cases where drug toxicity related to high toxic PDC is suspected. In addition, TDM can be used to establish whether or not optimum therapeutic drug concentrations have been achieved for drugs characterized by a response that is difficult to detect, or in which the

manifestations of disease are life-threatening and the trial and error approach to modification of dosing regimen is unacceptable.

Table1. Therapeutic drug monitoring data for drugs in dogs or cats

Drug	Dose[1] mg/kg	Route	Interval	Halflife	Time to SS[2]	Therapeutic Range (3) Low	High	Units
Bromide	20	PO	12-24hrs	21d	2-3m	1	3	mg/ml
Clorazepate	0.5-1	PO	8 hrs	4-6 (h)	<24 hrs	150[3]	400	ng/ml
Diazepam	1-2	PO	8 hrs		<24 hrs	150[3]	400	
	0.5-2[4]	IV	5-10 min					
	5 to 20[5] total	IV inf	60 min					
Felbamate	15	PO	divided bid	5-8 (d)	<24 hrs	30	60	mcg/ml
Gabapentin	10-30	PO	8-12	< 14 h	2 – 3 days	12	21	mcg/ml
Leviteracetam	20 mg/kg	PO	8	2-8h		6	21	mcg/ml
Phenobarbital	2	PO	12 hrs	app 72	2 to 3 w	20	45	mcg/ml
	3-6	IM		(9-12; d)	2-3 days			
	6-12[8]	IV slow	3 mg/kg increments to effect					
Zonisamide	4-6	PO	8-12	16-44*	2-3 days	10	40	mcg/ml

In situations in which chronic drug administration is expected, TDM can be used to define the effective target PDC in the patient. The target PDC can then be used if pharmacokinetics changes in the patient over the course of chronic drug administration due to disease, environmental changes, age, or drug (or diet) interactions. Drug monitoring has also been useful in identifying owner noncompliance as a cause of therapeutic failure or adverse reactions. Not all drugs can be monitored by TDM; certain criteria must be met. Patient response to the drug must correlate with (i.e., parallel) PDC. Drugs whose metabolites (e.g., diazepam) or for which one of two enantiomers composes a large proportion of the desired pharmacologic response cannot be as effectively monitored by measuring the parent drug. Rather, all active metabolites and/or the parent drug should be measured. For cyclosporine (CsA), for which parent and *some* metabolites are active, high-performance liquid chromatography (HPLC) measures only the parent whereas immunoassays measure parent and some metabolites. For many drugs, recommended therapeutic ranges in animals have been extrapolated from those determined in humans, but care must be taken with this approach (e.g., bromide and procainamide). The drug must be detectable in a relatively small serum sample size, and analytical methods must be available to detect the drug in plasma rapidly and accurately. Also, cost of the analytical meth-od must be reasonable. Special handling preparation is not generally necessary for TDM, although the laboratory should be called to confirm special handling procedures. Serum separator tubes should, however, be avoided for lipid soluble drugs. Serum separator tubes contain silicon, which may bind AED drugs. Either these tubes should not be used or serum should be withdrawn from the tube immediately after centrifugation.

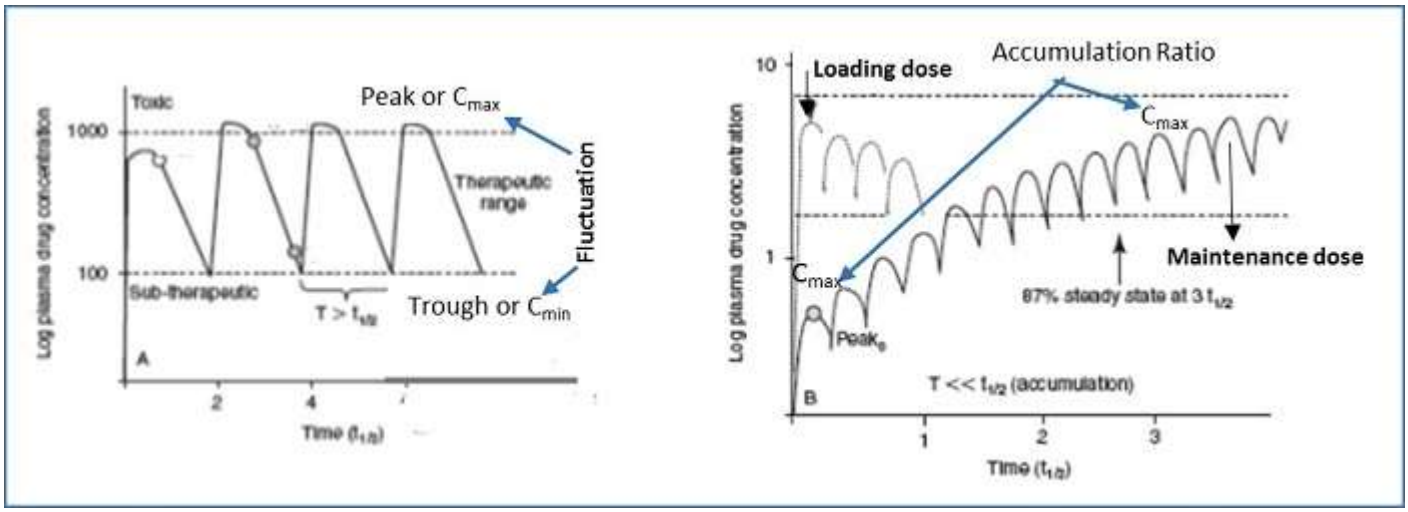
Implementation and response to TDM requires an understanding of the relationships between PDC, interval (T), and drug elimination half-life (t½). In general, TDM should not be implemented until PDCs have reached steady state in the patient. Steady state PDCs occur at the point when drug input and drug elimination (i.e., distribution, metabolism, and/or excretion) are equilibrated. Although PDCs change to some degree during the dosing interval, they remain constant between intervals at steady state (note that “steady state” is not actually reached with drugs whose half-life is substantially shorter than the dosing interval). With multiple drug dosing at the **same** regimen, PDC will reach 50, 75, and 87.5% of steady state concentration at one, two, or three half-lives, respectively (and so on), regardless of the drug. The same time period (i.e., 3–5 drug half-lives) must elapse prior to monitoring if any portion of the original dosing range (i.e., dose, frequency, or route) is changed.

Relationship between half-life and dosing interval: For drugs with a long t½ compared to the dosing interval, drug accumulation can be very dramatic (i.e., the drug concentrations following the first dose (PDC_{first}) are much lower than drug concentrations at steady state (PDC_{ss}). The dosing regimen of such drugs is designed such that drug concentrations will be in the therapeutic range, but only when steady state concentrations have been achieved. The amount that the drug accumulates depends on how much shorter the interval is compared to the t½ (ratio of T:t½).

Long half-life compared to interval: For drugs characterized by a long t½, TDM can be implemented by measuring concentrations at approximately one drug t½ at which time PDC will be approximately 50% of PDC_{ss}. A third alternative to proactive monitoring is available for patients for whom steady state concentrations must be reached immediately. A loading dose can be administered to rapidly achieve therapeutic PDC. After a loading dose is administered, the maintenance dose should be “just right” to maintain the PDC achieved after loading. If not, a problem may not become obvious until steady state occurs (i.e., 3 to 5 t½; for bromide, this is 3 months). However, monitoring can be used to evaluate the proper maintenance dose proactively.

When using a loading dose, TDM might be performed three times. Using bromide as an example, the first time is after oral absorption of the last dose of the loading dose is complete to establish a baseline (e.g., day 6). The second time would be one drug t½ later (e.g., 21 days) to assure that the maintenance dose is able to maintain concentrations achieved by loading. One drug t½ later is recommended because most of the change in drug concentrations that occur if the maintenance dose is not correct will be present at this time. If the second sample (collected at one drug t½) does not approximate the first (collected immediately after the load), the maintenance dose can be modified at this time rather than

waiting for steady state and the risk of therapeutic failure or toxicity. In general, monitoring of a drug with a long half-life requires only one sample. Generally, for consistency's sake, the author suggests collection of a trough (before the next dose).



Short half-life compared to interval: Many drugs are characterized by half-lives that are much shorter than the dosing interval. For these drugs, no to little accumulation occurs, the concept of "steady state" is perhaps irrelevant, and response can be evaluated with the first dose (or as soon as the disease has had time to respond). The amount that PDC declines during a dosing interval, that is, the fluctuation between C_{max}/C_{min}) depends, again, on the relationship between t½ and interval. If the interval is 1, 2, 3, or 4 times the t½, PDC will decrease 50, 75, 87.5 and 93.75%, respectively during the dosing interval. This fluctuation may be unacceptable (e.g., antiepileptics, some cardiac drugs, potentially cyclosporine) or acceptable (e.g., aminoglycoside drugs, which act irreversibly).

Detection of this fluctuation requires collection of both a peak sample and a trough sample. The peak PDC (C_{max}) is the maximum concentration achieved after a dose is administered, and presumably it should not exceed the recommended C_{max} if the drug is not safe. Timing of peak sample collection can be difficult to predict; ideally, absorption and distribution should be complete. The route of drug administration can influence the time at which peak PDC occurs, which varies among drugs. For orally administered drugs, absorption is slower (1–2 hours), and distribution is often complete by the time peak PDCs have been achieved. However, the ab-sorption rate can vary widely due to such factors as product preparation, the effect of food, or patient variability. Because food can slow the absorption of many drugs, fasting is generally indicated (if safe) prior to TDM; however, exceptions are noted for some drugs (i.e., imidazole antifungals).

Generally, peak PDCs occur 2–4 hours after oral administration. Some drugs are simply absorbed more slowly than others (e.g., phenobarbital, PB) and the time of peak PDC sample collection is longer (e.g., 2–5 hours for PB). Collection of peak and trough samples is particularly important for drugs characterized by a narrow therapeutic range and a short half-life. For such drugs, calculating the t½ might be useful for determining an appropriate dosing interval, although both a peak sample and a trough sample should be collected (t½=0.693/kel, where kel=LN(C1/C2)/t_2-t_1, where C and t are the concentration and time point of the first [peak] and second [trough] samples, respectively. This can be easily calculated using Microsoft Excel). In contrast to drugs with a short t½, peak and trough concentrations will not differ substantially for drugs whose t½ is much longer than the dosing interval (e.g., bromide and, for some patients, PB) and a single sample is generally sufficient for such drugs. Single samples might also be indicated for slow release products (e.g., slow-release levetiracetam) if constant drug absorption mitigates a detectable difference between peak and trough concentrations. If the question to be answered by TDM is one of toxicity, a single peak sample may answer the question; if efficacy, a single trough sample may, for example, for antiepileptics.

The "When to's" of Therapeutic Drug Monitoring

(1)"**Start-Up**." (a) Maintenance dose. Monitor at baseline in a responding animal to establish the therapeutic range for the patient. **(b) Loading dose or maintenance dose combination (including a "mini" loading dose)**: A sample should be collected after a loading dose has distributed (the day after loading bromide or at least 2 hours after loading with phenobar-bital) and at one half-life into the maintenance dose. If the two samples do not match, the maintenance dose should be proportionately adjusted. (c) For drugs with a long half-life, if a loading sample was not given, proactive monitoring can occur at one half-life (eg, 3 weeks for bromide). The results can be multiplied by 2 to determine the predicted steady state. (d) Establish baseline : A steady state sample should be collected once steady state has been reached.

(2) "**Check-up**." (a) Rechecks are indicated to proactively ensure that effective concentrations are maintained and safe concentrations are not exceeded. The frequency varies with the seriousness of therapeutic failure or the risk of toxicity. Intervals of 6–12 months are generally recommended for the well-controlled patient and 3–6 months for the poorly controlled patient. For immunomodulators, 3-week to 6-month intervals for life-threatening disease are recommended.

(3) "**What's up**." **(a) Establish a cause for therapeutic failure or to confirm toxicity**. For patients that have not responded well to a new drug or a new dose, despite doses at the mid to high end of the recommended dosing range, or in previously well-controlled patients that fail therapy or develop signs of adversity.

(4) "**Catch up**." (a) Any time a dosing regimen is changed, a new baseline should be established at steady state.

A number of factors can change a dosing regimen without the permission of the Veterinarians. These include **(b) changes in patient factors**: Progression or improvement of cardiac, renal, or hepatic disease; changes in clearance; and, to a lesser degree, volume of distribution may change elimination half–life and thus peak or trough concentrations. **(c) Detect drug–drug or drug–diet interactions**. Changes in diet or addition of a drug that may interact: baseline concentrations should be reestablished before and after a change, if there is a risk that the change in diet or drug therapies may alter the disposition of the drug of interest. For example, bromide should be measured before and at steady state after the administration of a new diet; phenobarbital should be monitored before and after beginning chloramphenicol or an imidazole antifungal; cyclosporine should be monitored before and after ketoconazole (or any imidazole) or azithromycin therapy is implemented, etc.

ANTICONVULSANT THERAPEUTIC DRUG MONITORING

Phenobarbital (PB): (15 to 45 mcg/mL; half-life 48 hours) Generally, a single trough sample should be sufficient for TDM. However, if induction of drug-metabolizing enzymes has occurred, the elimination half-life may be sufficiently short to allow excessive fluctuation in PDC during the dosing interval. This short half-life can be detected only if both peak and trough samples are measured. In a phenobarbital-naïve dog, or when phenobarbital doses are changed, baseline samples should be determined at steady state, 9–14 days after beginning therapy. A recheck trough sample 1–3 months later is prudent to detect induction. Many of the author's patients respond to phenobarbital at concentrations below the minimum therapeutic range of 15 µg/mL, which suggests that a lower therapeutic range may be indicated in dogs.

Bromide (BR): (1 to 3 mg/mL; half-life 21 days) Because the elimination half-life of bromide is so long, manipulating the dose before steady state is reached may be necessary for some patients. Collection of a sample at one half-life after the start of therapy (i.e., 3–4 weeks) can be performed to assess the dose proactively; doubling the 3-week concentration should approximate the steady state concentration. Baseline should be established at 2.5–3 months. If the patient is loaded, a sample should be collected the day after loading is complete and then at one half-life. The former sample is indicated to determine what the loading dose achieved and the latter to ensure that the maintenance dose is maintaining what the loading dose has achieved; the two samples should be within 15% of each other. If not, the maintenance dose can be adjusted proportionately. Note that a 3-week sample in a patient that received a loading dose is minimally useful without the post-load monitoring sample for comparison: concentrations may increase or decrease depending on the

accuracy of the maintenance dose. In all patients, regardless of the method of dosing, a final sample should be collected at steady state to establish baseline. Finally, if the maintenance dose is altered, a concentration might be measured at one half-life to assess the impact of the change proactively, but the minimum reassessment should occur at the new steady state (i.e., 2.5-3 months after the dose change). Additionally, bromide might also be checked before and after any change in diet or medication that impacts chloride excretion has occurred.

Zonisamide (ZN): (15 to 40 mcg/mL **initial** concentrations; half-life similar to phenobarbital). The half-life of zonisamide is generally longer than 24 hours; therefore, concentrations should not fluctuate sufficiently during a 12-hour dosing interval to routinely justify a peak sample and a trough sample. Because toxicity is not likely to be as great a concern as therapeutic failure, a trough sample is recommended for routine monitoring. In problematic patients a peak and a trough may be justified to rule out a short half-life as a contributing cause of difficult control. Currently, zonisamide is among the drugs for which the maximum therapeutic range that has been established in humans can be exceeded with minimal adverse effects in dogs.

Levetiracetam (LE): (15 to 45 mcg/mL, trough): The half-life of levetiracetam (standard release) can be as short as 1–2 hours. However, the half-life can be also longer than 8–10 hours; longer half-lives should be anticipated if the slow release preparation is used. Because the duration of the half-life is not known, peak and trough samples are recommended at the beginning of therapy to determine the half-life in patients. With a longer half-life, control is much more likely to be accomplished with an 8-hour dosing interval in a patient. Once the half-life is established, a trough sample is recommended if only single samples are to be collected. A mid-sample concentration has little to offer, particularly given that drug concentrations may drop 50% or more from mid-interval concentrations. Thus, it is prudent to identify the lowest concentration possible during the interval. The recommended therapeutic range should be targeted by trough, rather than peak, concentration. Note that in a drug with a very short half-life (e.g., 2 hours), peak concentrations in a patient may be as much as 8 times as high as trough concentrations. Levetiracetam is sufficiently safe that a high peak concentration is likely to be tolerated. Because drug concentrations do not accumulate with drugs administered at an interval substantially longer than the half-life, steady state does not occur. Therefore levetiracetam (or another drug with a short half-life) might be monitored in the first 3–5 days of therapy. Waiting one seizure interval to ensure that seizures are adequately controlled is reasonable. The approach for monitoring levetiracetam can be followed as with other anticonvulsants associated with a short half-life compared to the dosing interval (e.g., gabapentin), unless the drug is potentially toxic. In such situations, monitoring peak and trough concentrations routinely may be prudent.

Gabapentin: The half-life of gabapentin also is short, suggesting that both peak and trough samples be collected. Recommendations for collection are similar to those for levetiracetam.

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