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Contents

Principles of therapeutic drug monitoring: a case of drug-resistant epilepsy in a dog

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Drug analysis for purposes of monitoring therapeutic outcomes is not a common practice in veterinary medicine but may be extremely valuable in many circumstances including; clinical cases in which there is a poor correlation between dose and drug plasma concentration, and therapeutic or toxic effects, confirmation of drug-induced toxicity for medications with very low therapeutic indices, assessment of compliance with the drug administration and assessing the occurrence of drug-drug interactions. Therapeutic drug monitoring may also be indicated for patients with altered physiological states such as renal, thyroid and hepatic disease, and electrolyte imbalances. In this article, a clinical case of canine idiopathic epilepsy with an apparent resistance to antiepileptic drug therapy is used to illustrate some of the basic principles of therapeutic drug monitoring (TMD).

Case report: history, clinical presentation and treatment

Two years ago, a 4-year-old, male Staffordshire bull terrier, 24 Kg, was diagnosed with idiopathic epilepsy with a history of tonic-clonic seizures (~3 seizures per month). The seizures were characterised by facial automatisms, forelimb clonus, falling and loss of consciousness. Therapy was initiated with phenobarbitone 2.5 mg/Kg PO BID and the dose had been escalated and stabilised at 7 mg/kg PO BID for several months. The patient begun seizuring more frequently (~ 1 seizure per week) and was presented to James Cook veterinary hospital in status epilepticus and dilated pupils that did not respond to light. The referring doctor had administered 1 mg/kg diazepam but no response was observed. The patient was sedated with boluses of 20 mg of propofol at a time, and was also given 5 mg/Kg phenobarbitone intravenously BID, 0.005 mg/Kg/min midazolam over 6 hours, 4 mg/Kg furosemide intravenously and 1 gram/Kg of mannitol slowly intravenously over 30 minutes.

Blood analysis revealed no detectable abnormalities and Phenobarbital levels were within therapeutic range. The rest of the neurological examination could not be performed because of anaesthetics. Oxygen saturation (SPO_2) was estimated at 88% and oxygen supplementation was instituted. The animal did not seizure again, had normal papillary light responses and did not appear to be blind. The
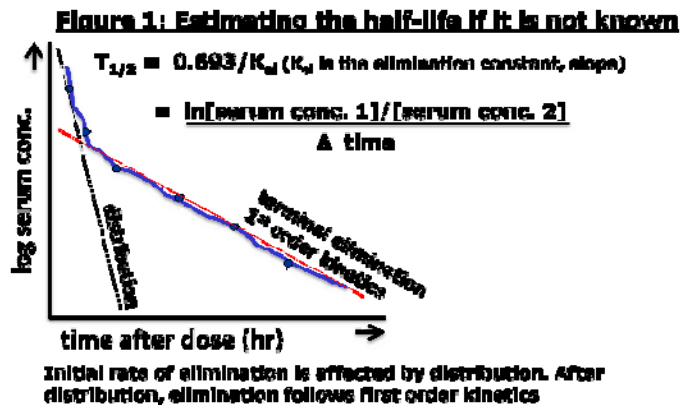
immediate concerns were the recurrence of frequent and severe convulsions. As a result, plans were made to send the patient home with strong considerations of the application of the principles of therapeutic drug monitoring. In addition, magnetic resonance imaging of the brain and spinal cord was sought.

What principles of TDM are applicable to the use of phenobarbitone in this case?

When to institute TDM, when and how to sample blood for drug analysis:

Many drugs may be used to treat canine idiopathic epilepsy but phenobarbitone and potassium bromide are the most commonly prescribed for this condition.[1-2] However, both phenobarbitone and the bromide have variable pharmacokinetic profiles in different dogs and each individual animal may show variable rates of absorption, distribution, metabolism and excretion. This results in variable serum drug concentrations even at recommended dose rates (2-4 mg/kg body weight per day divided into q8 or 12h) for phenobarbitone.[3-4] The average half-life ($T_{1/2}$) of phenobarbitone is 53 hr (32-75 hr) and with repeated dosing at intervals shorter than the half-life, the drug accumulates until "steady state" is attained. At steady state, drug intake equilibrates with elimination by metabolism and excretion and serum drug concentrations will only fluctuate between given limits of minimum (C_{min}-troughs) and maximum (C_{max}-peaks). It takes ~5-6 half-lives to attain 99% of steady-state serum drug concentrations and in the case of phenobarbitone ($T_{1/2}$ = 53 hr), TDM may be instituted **11-14** days after the initiation of therapy. If $T_{1/2}$ is markedly shorter (< 24 hours) with the accompanying lack of efficacy, peak (4-5 hr after dosing) and trough serum concentrations (taken just before the next dose) could be measured to ascertain the exact $T_{1/2}$ and an appropriate dosing interval. This procedure is illustrated in **Figure 1** below. For animals with $T_{1/2}$ of phenobarbitone < 24 hr, dosing every 8 hours may improve seizure control. Either serum or plasma sampled any time during the dosing interval could consistently be used for drug analysis because phenobarbitone has a relatively long half-life implying that variations between peaks and troughs are minimised. It is important to remember to avoid using serum-separator tubes because they decrease drug concentrations by adsorption of drug into the matrix.[5]

Figure 1: Estimating the half-life if it is not known

$$T_{1/2} = 0.693/K_{el} \text{ (}K_{el} \text{ is the elimination constant, slope)}$$

$$= \frac{\ln[\text{serum conc. 1}]/[\text{serum conc. 2}]}{\Delta \text{ time}}$$

log serum conc.

time after dose (hr)

Initial rate of elimination is affected by distribution. After distribution, elimination follows first order kinetics

Another important pharmcodynamic feature of phenobarbitone is its ability to induce the expression of cytochrome P450 enzymes (CYP2B11, CYP3A12 & CYP4A) via the retinoid receptor in hepatocytes and other tissues.[6] These functionalisation phase-1 enzymes are involved in the metabolism and clearance of this drug thus with repeated dosing, the metabolic clearance of phenobarbitone is markedly enhanced and this may alter steady state serum concentrations. Typically, significant enzyme induction is detected 8-12 weeks after the initiation of therapy and routine monitoring is done every 6 months.[3] On the other hand, marked elevation of serum phenobarbitone concentrations is associated with hepatotoxicity characterised by increased serum concentrations of alkaline phosphatase and alanine transaminase.[7] As a consequence, hepatotoxicity will often limit the clinical use of phenobarbitone in chronic conditions and it usually recommended to add bromide therapy before reaching the upper limits of the therapeutic range.[7]

Interpretation of results of therapeutic drug monitoring:

Normal therapeutic serum concentrations of phenobarbitone are dependent on whether the patient is receiving monotherapy or drug combinations. For dogs on phenobarbitone only, **65-175** µmoles/L is recommended while for a combination of phenobarbitone and potassium bromide, **43-155** µmoles/L of phenobarbitone and **10-20** mmol/L (**1-2** mg/mL) of the bromide are believed to be within the therapeutic range.[4] Phenobarbitone may be reduced or removed from seizure therapy once the bromide ($T_{1/2}$ = 24 days), has attained steady state (~ 4 months). Typically the phenobarbitone dose is reduced by 10-25% every 4-6 weeks and the bromide is maintained at a serum concentration of **30** mmol/L.[8] To circumvent the problem associated with longer waiting periods to establish steady state, loading doses are usually given in dogs with severe and frequent seizures to allow for the rapid switch from one drug to another. A loading dose is intended to fully occupy the apparent volume of distribution of the drug to achieve a target, recommended therapeutic serum concentration (**1-2** mg/mL). The apparent volume of distribution of potassium bromide is (**0.2-0.4** L/Kg). So for the **24** Kg male dog described here, the recommended loading dose was evaluated as illustrated in **figure 2** below.

Figure 2: Pharmacokinetic principles & the loading dose

Loading dose = Volume of distribution * target serum concentration
= (0.2-0.4) L/Kg * 24 Kg * (1000-2000) mg/L
= (400-800) mg/Kg
Maintenance dose = Clearance (L/hr/Kg) * Weight (Kg) * target conc. (mg/L)
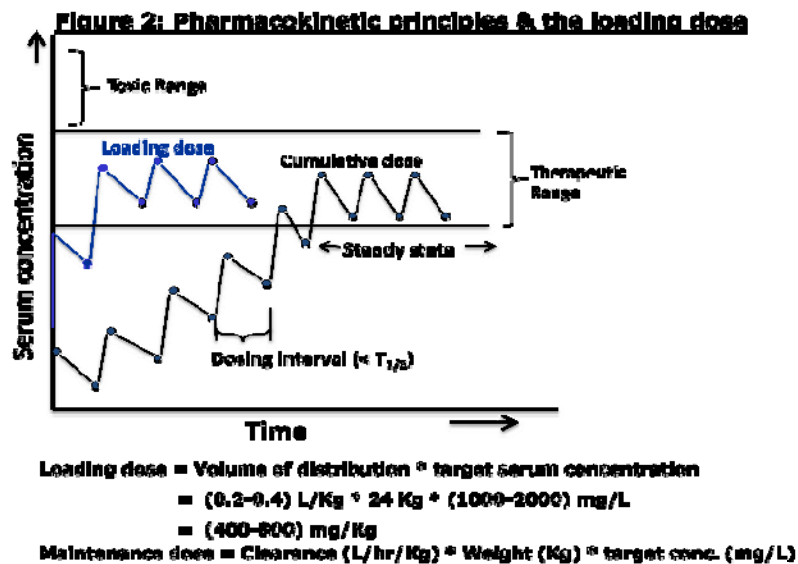
An oral loading dose of **600** mg/Kg of potassium bromide was divided into 5 doses, mixed with food and given over 5 days SID, followed by an initial maintenance dose of **30** mg/kg PO once daily. Typically a maintenance dose is based on the target plasma concentration and the clearance of a

particular drug. This dosing regimen was consistent with standard recommended doses for potassium bromide in treating idiopathic epilepsy.[1] Steady- state serum concentrations with the bromide were established and phenobarbitone was withdrawn. The patient stabilised for three months but suffered massive breakthrough seizures and because of the deteriorating quality of life and the cost of treatment he was euthanized.

Dose adjustment and increasing target serum drug concentration of an antiepileptic drug:

At the initiation of therapy, the patient described here received phenobarbitone at a rate of 2.5 mg/Kg PO BID and the dose had been escalated and stabilised at 7 mg/kg PO BID for several months. This section examines standard considerations and approaches in using TDM in adjusting the patient's dosing regimen. The first dosing rate (2.5 mg/Kg PO BID), yielded an average peak and trough serum phenobarbitone concentration (60 µmoles/L) below the recommended therapeutic range. Subsequently, we aimed to elevate the average serum concentrations to 170 µmoles/L. What should have been the corresponding adjusted dosing rate?

At steady state,

Rate of administration = elimination rate

Elimination rate = K*(serum concentration).

$$\frac{(\text{New dosing rate})}{(\text{Target serum conc.})} = \frac{(\text{Current dosing rate})}{(\text{Observed serum conc.})}$$

$$(\text{New dosing rate}) = \frac{(2.5 \text{ mg/Kg}) * (170 \text{ µmoles/L})}{(60 \text{ µmoles/L})}$$

New dosing rate = 7.08 mg/Kg PO q. 12 hr

It is important to note that phenobarbitone serum drug concentrations exceeding 180 µmoles/L may manifest in toxicity characterised by excessive sedation, ataxia, elevated alkaline phosphatase and hepatotoxicity, blood dyscrasias and polyphagia. Under these circumstances, phenobarbitone therapy alone may be inadequate and switching to other drugs may be recommended. Recent studies have documented the clinical use of other medications including primidone, levetiracetam, gabapentin, felbamate, clorazepate and zonisamide.[1,2,9]

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