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THERAPEUTIC DRUG MONITORING

This newsletter summarizes information on therapeutic drug monitoring (TDM) provided at the recent Antech Medicine Consultants Conference with Dr. Dawn M. Boothe of Texas A&M University.

GENERAL PRINCIPLES OF TDM

- Time of patient sampling for TDM.** Whether peak or trough drug concentrations are measured is influenced by the need for evaluating efficacy (trough) or safety/toxicosis (peak). If only a single sample will be collected, trough samples are generally preferred for consistency over time. Further, the time of peak plasma drug concentration (PDC) is more difficult to establish.
- Importance of elimination half-life ($t_{1/2}$).** Drugs with short $t_{1/2}$ times should have two samples drawn (e.g. diazepam, thyroxine), whereas those with long $t_{1/2}$ times need only a single sample (e.g. bromide, most dogs on phenobarbital).
- Sample handling.** Remember that blood samples for TDM should be placed in plain red top tubes (RRT) and **not** in serum separator tubes (SST).
- Concept of steady state concentrations.** Steady state PDCs occur when drug input and elimination by metabolism and/or excretion are equilibrated. Although PDCs change somewhat during the dosing interval, these changes remain consistent at steady state (i.e. both the peak and trough concentrations stay consistent).
 With repeated drug dosing, PDCs will reach 50% of their steady state concentration at one $t_{1/2}$, 75% at two $t_{1/2}$, 87.5% at three $t_{1/2}$, etc. Thus, steady state concentrations are

attained after 4-5 $t_{1/2}$ when the drug is administered with a fixed dosing regimen.

Evaluation of a drug's efficacy is often inappropriate until steady state has been reached, because only then will the maximum peak and trough concentrations and clinical response have been achieved.

PHENOBARBITAL

The $t_{1/2}$ is 32-75 hours in most dogs, although some patients can have a shorter $t_{1/2}$ such as <24 hours or even <12 hours.

Peak and trough concentrations should be measured initially, or when there is difficulty controlling seizures. Calculation of the $t_{1/2}$, which allows more accurate determination of the proper dosing interval, can be made as follows:

$$t_{1/2} = \frac{0.693}{K_{el}}$$

Where K_{el} = slope of drug concentration (elimination constant) vs time line

$$= \frac{\ln [\text{concentration 1} / \text{concentration 2}]}{\text{time 2} - \text{time 1}}$$

Example:

$$\begin{aligned} \text{time 1 (6 hr)} &= 25 \mu\text{g/mL} \\ \text{time 2 (12 hr)} &= 10 \mu\text{g/mL} \\ K_{el} &= \frac{\ln [25/10]}{(12 - 6)} = 0.15 \end{aligned}$$

$$t_{1/2} = \frac{0.693}{0.15} = 4.6 \text{ hr}$$

If the $t_{1/2}$ of phenobarbital is <24 hours, then dosing every 8 hours may improve seizure control.

Monitoring Recommendations. At 2 weeks, perform peak (4-5 hours) and trough (just prior to next dose) concentrations to deter-

THERAPEUTIC DRUG MONITORING (CONT'D.)

mine $t^{1/2}$ and optimal dosing interval. At 8-12 weeks, perform trough measurement to detect induction. At 6 month intervals, measured trough concentrations, although this may not be an essential time as data show peak and trough concentrations at steady state are not appreciably different. Anytime a patient experiences "break-through" seizures, measure peak and trough drug concentrations.

Phenobarbital and Pancreatitis. There are anecdotal reports of pancreatitis in dogs receiving phenobarbital or bromide, but there is no documentation of a cause-and-effect relationship. When present, pancreatitis may be secondary to polyphagia.

BROMIDE

The $t^{1/2}$ is about 24 days. Steady state concentrations are not reached for at least 2-3 months.

Loading with bromide. This procedure is recommended in the following situations:

- cluster seizures
- when patient on phenobarbital needs to be weaned off quickly because of hepatotoxicity

The loading dose is designed to establish steady state concentrations immediately rather than in 2-3 months needed with maintenance therapy. To achieve ~ 1 mg/mL PDC, a loading dose of 450 mg/kg split and administered over 5 days is needed. The maintenance dose (~ 30 mg/kg to maintain a PDC of ~ 1 mg/mL) needs to be given along with the loading dose.

Higher doses are needed to quickly achieve and maintain higher target concentrations (e.g. 600 mg/kg loading and 40 mg/kg maintenance to achieve and maintain ~ 1.5 mg/mL).

Maintenance. Most animals achieve or maintain bromide concentrations of 1 mg/mL on a maintenance dose of 30 mg/kg/day.

Monitoring. *With loading doses:* PDCs should be measured one day after loading to verify that the target is reached. If drug concentration is too low, a second smaller loading dose can be given. A general rule of thumb is that a loading dose of 250 mg/kg will increase drug concentrations by ~ 0.5 mg/mL. Drug concentrations should be checked again 1 month later to verify that the target maintenance dose is achieved.

Without loading doses: measure drug concentrations 3-4 weeks after starting treatment. At that

time (one $t^{1/2}$), drug concentrations will be about half of steady state, and so the maintenance dose can be modified, if needed.

Bromide and pancreatitis. See above comments for phenobarbital.

Bromide in cats. Maintenance dosing at 30 mg/kg/day can be used safely in cats. Steady state is reached at 8 weeks, and $t^{1/2}$ is about 10 days. Respiratory disease has been seen in cats receiving bromide. In one case series, 10/17 cats (58%) on bromide had episodes of coughing which resolved in two cats when bromide was discontinued.

THEOPHYLLINE

The brand name sustained release theophylline products are no longer available. Generic preparations may not be equally bioavailable, and so monitoring of trough concentrations is advised to ensure that the therapeutic range is achieved.

Monitoring.

Cats: 24 hour pre-medication trough is measured.
Dogs: 12 hours pre-medication trough is used. The therapeutic range is 10-20 μ g/mL.

DIGOXIN

The elimination $t^{1/2}$ is about 30 hours in most dogs and cats. Some animals can have a short $t^{1/2}$ which can present problems when monitoring drug concentrations.

With long $t^{1/2}$, a 6-8 hour post-pill sample is fine to check peak digoxin concentrations.

With short $t^{1/2}$, the peak may occur as early as 3 hours post-pill. In these cases, the 6-8 hour post-pill sample will not reflect the peak amount and there is a risk of toxicosis, if dose is subsequently increased.

CYCLOSPORINE

The elimination $t^{1/2}$ is short, and may even be only 1-2 hours. A 12 hour dosing interval is still acceptable because of its residual effects.

Monitoring. Measuring cyclosporine can be with RIA or HPLC methods, the former being much less expensive. Whole blood samples must be used here. Target trough concentrations are 400-600 ng/mL, although lower concentrations may be sufficient for some diseases. Experience in treating dogs with perianal fistular indicates that a clinical response begins once their trough cyclosporine concentrations reach 300-400 ng/mL.

Micro Morsel

Antech clients have requested sensitivity studies and discs for marbofloxacin. The manufacturer (Pfizer) has indicated that sensitivity discs for this antibiotic are in the final phases of quality control and should be released shortly. As soon as they become available, Antech will offer this option.

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