

THERAPEUTIC DRUG MONITORING

Guidelines for drug monitoring are listed in the accompanying table. Veterinarians can utilize local hospitals and diagnostic laboratories that have the capability of performing drug analysis. Because of large inter-individual variations in pharmacokinetics for the drugs listed, monitoring is advised for the following conditions: (a) animal refractory to medication, despite an adequate dose, (b) animal showing toxicity, despite an adequate dose, (c) assessing owner compliance, (d) switching medications (eg from a brand name to a generic and need to establish a baseline, (e) check for drug interaction, (for example to check to see whether or not interactions are occurring with cyclosporine administration) and (f) examine individual patients for pharmacokinetic differences such as altered absorption or elimination.

THERAPEUTIC DRUG MONITORING: CONSIDERATIONS

Timing of Sample:

For short half-life drugs, more than one sample (three is ideal) is the most useful for determining individual pharmacokinetic parameters. Alternatively, a peak (C_{MAX}) and a trough (C_{MIN}) can be collected to determine the bounds of high and low concentrations at steady-state. For long half-life drugs (digoxin, bromide, phenobarbital), a single sample during the dosing interval is sufficient. If one suspects altered clearance rates, more samples can be collected to assess half-life, however. For cyclosporine, a single trough sample has been used for many years, but now recommendations are changing to a single two hour sample (C_2). For cyclosporine a “trough” usually refers to a 12 hour sample, even though this drug is used once a day, or once every other day in some patients.

Assay:

The assay will vary according to the laboratories. Many automated chemistry machines used for biochemical analysis have drug detection kits that can be added to their menus. Some laboratories use RIA methods, others use other immunoassay methods (eg, chemiluminescence). One of the popular bench-top assay machines is the fluorescence polarization immunoassay by Abbot, known commonly as the TDx method. Rarely is HPLC used because of the expense and slow turn-around time, but it is still considered the gold standard for specificity. This assay reports a true value, except for cyclosporine. For cyclosporine, the TDx assay overestimates the true value in dogs and cats. Therefore, in cats the TDx value should be multiplied by a factor of 0.5 to get the true value. For dogs, multiply the TDx value by 0.65 to get the true value.

Type of Sample:

The type of sample will vary according to the specific assay. Most assays allow serum, some require plasma, and for some assays either is acceptable. Samples should be collected and centrifuged as soon as possible. Avoid serum-separator tubes because these may lower drug concentrations by adsorbing drug into the matrix. Some assays are specific about storage of samples. Plastic cryo-vial type tubes are acceptable for most assays. For cyclosporine, the assay specifically calls for whole blood, not plasma, collected in and EDTA tube.

Examples of drugs that can be measured in most routine clinical or diagnostic laboratories are listed in the accompanying table.

Test	Specimen	Timing of Sample	Tube	Storage	Effect of Interference	Reference Range
Amikacin	serum or plasma 0.5 mL	1, 2, and 4 hours after dose, preferably. Other strategies for collecting two or three samples also have been used to assess clearance.	red-top or lavender-top	30 days @ -20C	Hemolysis: no effect; Icterus: no effect Lipemia: no effect Cross reactivity: < 1% interference with other drugs and antibiotics, except tobramycin, which which there is high cross-reactivity. Limit of detection: 0.8 mcg/mL	Peak 40 mcg/ml Trough < 0.8 mcg/ml **Other methods to assess clearance are possible if more than two samples are collected.
Bromide (potassium or sodium bromide)	Serum 0.5 mL	Anytime during dosing interval.	red-top	60 days @ -20C	No interference with other drugs. Bromide and phenobarbital can be analyzed in same sample. Hemolysis: no effect Icterus: no effect Lipemia: no effect	100 - 200 mg/dl (with phenobarbital) 200 -300 mg/dl (monotherapy)
Cyclosporine	whole blood 1.0 mL	Trough (12 hours after last dose). Alternatively, peak concentrations at 2 hours have been used.	lavender-top	30 days @ -20C	* Because of metabolites, the assay overestimates true cyclosporine concentrations by 1.5-2x. For a true level, correct result by x 0.7 in dogs; and x 0.5 in cats.	300-600 ng/mL @ 12 hr. (may vary with disease)
Digoxin	Serum 0.5 mL	Anytime during dosing interval. Generally 4-6 hours after dosing.	red-top	7 days @ 2-8C 2 months @ -20C	Hemolysis: no effect; Bilirubin: No effect Lipemia: No effect Heparin tube: decrease by 5% EDTA tube: decrease by 7% Do not use serum-separator tubes.	0.8 - 2.5 ng/ml

Gentamicin	serum or plasma 0.5 mL	1, 2, and 4 hours after dose, preferably. Other strategies for collecting two or three samples also have been used to assess clearance.	red-top or lavender-top	30 days @ -20C	Hemolysis, Icterus, Lipemia produce < 5% error in the assay. Cross reactivity: < 1% interference with other drugs and antibiotics. Limit of detection: 0.27 mcg/mL	Peak: 20 mcg/mL Trough: < 0.27 mcg/ml *Other methods to assess clearance are possible if more than two samples are collected.
Phenobarbital	serum or plasma 0.5 mL	Anytime during dosing interval.	red-top, or lavender-top	2 days @ 2-8 C 1 month @ -20C	Bilirubin: no effect; Hemolysis: no effect EDTA or Heparin Tube: no significant effect. Do not use serum-separator tubes.	15 - 40 mcg/ml
Theophylline	serum 0.5 mL	Ideally, a peak and trough should be collected. If that is not possible, collect a trough immediately before the next dose.	red-top	30 days @ -20C	Hemolysis, Icterus, produce < 5% error in the assay. Lipemia produces <10% error. Cross reactivity: < 1% interference with other drugs, and 1.5% cross reactivity with theobromine. Limit of detection: 0.82 mcg/mL	10 - 20 mcg/ml. In some patients, trough concentrations of 5 mcg/mL have been effective.
Vancomycin	Serum 0.5 mL		red-top	30 days @ -20C	Hemolysis, Icterus, Lipemia produce < 5% error in the assay. Cross reactivity: < 1% interference with other drugs, and 1.5% cross reactivity with theobromine. Limit of detection: 2.0 mcg/mL	Peak: 30-40 mcg/mL Trough: 5-10 mcg/mL

Where and When to Submit Samples:Samples for cyclosporine analysis can be sent to:

College of Veterinary Medicine

Veterinary Teaching Hospital

North Carolina State University

4700 Hillsborough Street

Raleigh, North Carolina 27606

Phone: 919-513-6385

Attn: Ms. Lyndy Harden, Room C268, Clinical Pharmacology Laboratory; phone 919-513-6565

What to Collect:

Check table above for sample type to collect. If shipping, transfer sample to a sturdy tube that will withstand mailing to avoid breakage.

Samples may be frozen or kept cold in refrigerator until analysis. Check table for stability under freezing.

Check our web site for current charges: <http://www.cvm.ncsu.edu/vth/vthsupportclinicalpharmacology.htm>

When do I get results:

Samples are typically run every other day unless there is an urgent need for immediate results.

If a fax number or e-mail is included with the sample, results can be sent to the referring veterinarian. Otherwise, please specify the method of reporting you prefer when submitting samples.