

THERAPEUTIC DRUG MONITORING: Cyclosporine
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A common oral dose in people is 5-10 mg/kg/day to achieve targeted whole blood concentrations of 150-400 ng/ml. In people, dosages are adjusted to meet the needs of the individual patient on the basis of clinical response and monitoring trough plasma concentrations. For animals, doses of 10-20 mg/kg/day were frequently cited in older publications, but more recent recommendations, in which newer formulations have been used cited lower doses. For organ transplantation in cats (Mathews and Gregory, 1997) a dose of 3 mg/kg q12h of the Neoral formulation (dose was doubled for Sandimmune formulation) was used to achieve trough blood concentrations of 300-500 ng/ml. At NCSU we routinely administer 25 mg/cat for suppression of immunity for transplantation, and modify as needed with monitoring. For organ transplant in dogs, 10 mg/kg q12h to achieve concentrations of 500-600 ng/mL has been used (Mathews et al, 2000). A report on treating perianal fistulas in dogs (Mathews and Sukhiani, 1997) found that an average dose of 6 mg/kg q12h was needed to achieve a targeted blood concentration of 400-600 ng/ml. However, this recommendation was later modified to 2.5 to 6 mg/kg/day (3 mg/kg q12h) to achieve an effective blood concentration of 100-300 ng/ml. For dogs when treating perianal fistulas we have achieved adequate blood concentrations, without producing toxicity, at a dose of 3 mg/kg q12h.

For treating dermatitis in dogs, the effective dose has been 5 mg/kg/day. Some clinicians have been able to lower the dose, or administer the dose every other day, and still maintain clinical remission. The pharmacokinetics of cyclosporine in treated animals has been examined (Steffan et al, 2004). In their study, they found that routine monitoring of cyclosporine in dogs with atopic dermatitis was not necessary. When animals were administered a dose of 5 mg/kg/day, there did not appear to be a strong correlation between blood concentration achieved and clinical response. Nevertheless, because of wide individual variation in cyclosporine pharmacokinetics, monitoring has been used to determine the optimum dose for each patient. According to one paper, clinical benefits have not been observed when trough concentrations have fallen below 50 ng/mL, therefore blood testing of patients failing therapy was suggested to reveal inadequate dosing (Robson & Burton, 2003).

Cyclosporine is available in human formulation capsules of 25 and 100 mg, 20 mg/mL oral solution, and 50 mg/mL injection. The veterinary brand (Atopica) is available as 10, 25, 50, and 100 mg. There are also generic preparations available, but their absorption and pharmacokinetics have not been reported for animals. Some comparisons have not demonstrated that the generic formulations are significantly less expensive than brand name products.

Assay Specificity:

One must be cognizant of the assay used when monitoring cyclosporine. Plasma values will be lower than whole-blood assays because as much as 50-60%, and 10-20% of the dose is concentrated in erythrocytes and leukocytes, respectively. Nonspecific assays will report higher values than a more specific (monoclonal or HPLC) assay. Despite the hypothesized higher specificity when using the monoclonal assay, important discrepancies between these assays and the more specific HPLC assay have been reported (Steimer 1999). For example, in people the difference between HPLC and the commonly-used TDx monoclonal immunoassay was 57%. In cats, we found that the TDx assay overestimated the true cyclosporine concentration by a factor

of approximately 2 fold. (That is, TDx assay reporting 500 ng/ml corresponded to an actual value of 250 ng/mL). In dogs, the TDx assay overestimates the true cyclosporine concentrations by a factor of 1.5 to 1.7 (Steffan et al, 2004). When using a specific radioimmunoassay or HPLC true concentrations are measured. But, when using a TDx fluorescence polarization assay (monoclonal whole blood) multiply the feline concentrations by 0.5 to get the true concentration, and multiply the canine concentration by 0.6 to get the true concentration.

Timing of Sample:

Most recommendations have been based on trough blood sample monitoring. Trough samples are collected immediately before the next scheduled dose; therefore the sample is either 12 or 24 hours after the last dose. These recommendations are being modified in human medicine to a recommendation of a two-hour sample (C_2). Apparently there is evidence that a C_2 blood sample value correlates better with clinical results than trough samples (Levy et al, 2002; Nashan et al 2002). In cats, levels are approximately twice as high at two hours compared to the levels at 12 hours (Mehl, et al 2003).

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

What to Collect:

Minimum of 0.5 mL (½ cc) whole blood, collected in purple-top tube. Sample should not be centrifuged.

Sample may be frozen or kept cold in refrigerator until analysis.

Samples are stable for 30 days at -20°C (frozen).

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

When do I get results:

Samples are typically run on every Friday 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.

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