

PRACTICAL GUIDELINES FOR TACROLIMUS AND CYCLOSPORINE USE

Tacrolimus (TAC) and cyclosporine (CsA) are narrow therapeutic index drugs with significant inter-patient variability in their pharmacokinetics. Pediatric patients demonstrate faster absorption, faster clearance and altered volume of distribution with both TAC and CsA compared to adults. Dosing of these medications must be individualized and guided by therapeutic drug monitoring.

MONITORING TACROLIMUS AND CYCLOSPORINE LEVELS:

1. LAB ASSAY:

Whole blood TAC and CsA samples are sent to VGH for processing using a tandem mass spectrometry assay.

2. TIMING OF SAMPLES

For oral dosing, trough levels should be drawn consistently 0-60 minutes prior to the morning dose, to minimize variation.

Pharmacokinetic sampling to calculate AUC (area under the curve) requires blood sample draws at pre-specified time points and are dependent on drug and formulation used. Consult pharmacist for guidance.

For continuous IV infusions: samples may be drawn at any time. Note: target drug levels for continuous IV infusions differ from standard targets for solid organ transplant, consult pharmacist for guidance. Target drug levels for HSCT are the same for continuous IV infusion and other routes of administration.

3. DRAWING OF SAMPLES

If the patient has a double lumen CVC (central venous catheter), the sample should not be drawn through the lumen through which CsA or TAC is administered. If CsA or TAC are administered via continuous infusion, the infusion should be stopped for 5 minutes prior to drawing the sample.

If the patient has a single lumen CVC, draw the sample peripherally.

4. DRUG DOSING CONSIDERATIONS

- a. Interpret drug levels and adjust dose in the context of steady state. Note that TAC and CsA require 2-3 days to achieve steady-state.
- b. Assess for changes that may impact drug absorption or metabolism prior to adjusting doses (eg. drug interactions, food intake, gastrointestinal disease)
- c. Dose changes are generally limited to +/- 10-15% of the previous dose for routine monitoring, unless a specific reason to justify larger dose changes exists.
- d. Due to the linear relationship between dose and trough level, dose changes may be calculated as follows:
New dose = previous dose * ((trough target) / (measured trough))

5. CONVERTING TO IV:

The intravenous dose of cyclosporine (Sandimmune IV®) is one third the oral cyclosporine (Neoral®) dose. It may be administered IV via continuous infusion or given over 2-6 hours.

The intravenous dose of tacrolimus is one third the oral dose for solid organ transplant and one fourth for HSCT. It may be administered IV via continuous infusion or given over 4 hours. IV intermittent dosing is associated with increased risk of adverse effects due to high peak concentrations.

6. ADMINISTRATION CONSIDERATIONS:

Refer to the product monograph for additional administration instructions

CYCLOSPORINE LIQUID

- a. Use syringe provided by manufacturer to measure dose. Dry the outside of the syringe after use. Do not rinse with water. If the manufacturer syringe or glass dropper is not available, a standard plastic oral syringe may be used; draw the first dose into the plastic syringe, and discard, to allow binding to become saturated with drug. Do not wash syringe between uses.
- b. Administer the dose from a glass or ceramic cup (not plastic, Styrofoam, or paper). Mix dose in apple juice or orange juice (NOT grapefruit juice) or a soft drink if needed. Stir well and drink at once. Rinse glass with more diluent and drink to ensure total dose is taken. Always use the same liquid when giving the dose to minimize variation with drug absorption
- c. Mixing milk with CsA liquid should be avoided as it is unpalatable.
- d. Enteral feeding tube administration: There is minimal data relating to enteral feeding tube (such as G-tube) administration of CsA, however, enteral administration may sometimes be required. If so, measure the dose and administer it through the tube, and flush the tube immediately afterward with a sufficient volume of an appropriate diluent.

CYCLOSPORINE CAPSULES

- a. Leave the capsules in the foil wrapper until the time of administration.

TACROLIMUS LIQUID

- a. Enteral feeding tube administration: Oral administration of TAC is preferred. Enteral feeding tube administration may produce unpredictable drug absorption and labile drug levels. Administration of TAC through feeding tubes, however, may sometimes be required. If so, measure the dose and administer it through the tube, and flush the tube immediately afterward with a sufficient volume of an appropriate diluent.

TACROLIMUS CAPSULES

- a. Immediate release capsules (eg. Prograf) are NOT interchangeable with extended-release products (Advagraf or Envarsus XR)
- b. Immediate release capsules may be opened and contents mixed with water and flushed through enteral feeding tubes or taken orally. Extended-release products must be swallowed whole.

7. DRUG INTERACTIONS

TAC and CsA are primarily metabolized by the hepatic CYP450 enzyme system, and have many known interactions. The risk of drug interactions should be considered prior to new medications being introduced in patients receiving TAC or CsA.

TAC and CsA may interact with medications that increase or decrease their metabolism, leading to either risk of toxicity or lack of effect. TAC and CsA also have additive nephrotoxic risk when combined with certain drugs such as aminoglycosides or NSAIDs.

Grapefruit and grapefruit juice interact with TAC and CsA, and should be avoided while taking these medications.

For a complete list of drug interactions, refer to tertiary references or BC Transplant Guidelines.

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