PRACTICAL GUIDELINES FOR CYCLOSPORINE USE

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Cyclosporine is a challenging drug to use in clinical practice because of wide variability in the dose and the concentration measured in the blood. In the pediatric patient, dosing is made even more difficult because these patients exhibit different pharmacokinetics compared with adults: faster absorption, faster clearance and altered volume of distribution. The following information provides guidelines only, but reflects current practice at Children's Hospital.

MONITORING CYCLOSPORINE LEVELS:

1. ASSAY METHOD USED AT CHILDREN'S HOSPITAL

Cyclosporine (CsA) levels are measured by tandem mass spectrometry and is free from metabolite interference.,

2. TIMING OF SAMPLES

Be consistent with timing (e.g. always before the morning dose) to minimize variation.

For intermittent PO or IV dosing: draw morning trough concentration (before the morning dose).

For $AUC_{0\text{-}12}$ (area under the curve from 0-12 hours) calculations: draw the morning trough (C_0) and the 2 hour post dose (C_2) concentrations around the morning dose. *[reference: Pediatr Transplantation 2005: 9: 566-573. Strong DK, Lai A, Primmett D et al.]*

For continuous IV infusions: draw morning concentration.

3. DRAWING OF SAMPLES

If the patient has a double lumen CVC (central venous catheter), the sample should be drawn from the lumen OTHER than the one through which the CsA (cyclosporine) is administered. If CsA is being administered via continuous infusion, the infusion should be shut off for 5 minutes before drawing the sample.

If the patient has a single lumen CVC, the sample should be drawn peripherally.

4. PRACTICAL GUIDELINES FOR DOSE CHANGES

a. To alter the CsA blood concentration, change the dose by 10%, rounding off to the nearest 5 or 10 mg. Do not change the dose more than 20% at any single time. The new steady-state blood concentration will not be reached until approximately 2 - 3 days after a dose change, and blood concentrations should not be measured until steady-state is reached.
b. If a stable blood concentration changes suddenly, check for a new drug interaction before altering the dose (see 7, below).

5. TARGET LEVELS

Refer to Therapeutic serum Concentrations on page 224

6. CONVERTING FROM IV TO PO ROUTE

When changing from IV cyclosporine to oral cyclosporine (Neoral^{R}) the IV dose is multiplied by three as the oral bioavailability of cyclosporine is about 30%. It is recommended to obtain blood CsA concentrations 4 to 8 days after switching to PO to ensure a similar CsA blood concentration is obtained.

7. ORAL CYCLOSPORINE (Neoral[R])

LIQUID

a. Always measure the liquid using the supplied "pipette", and remember there is only 1 pipette per bottle, so don't throw it away. Dry the outside of the pipette after use. Do not rinse with water or any other liquid.
b. If the dose is < 1 mL, use the 1 mL pipette supplied by the manufacturer or a 1 mL tuberculin syringe to measure it. Administer the dose immediately after drawing up.
c. 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). Stir well and drink at once. Rinse glass with more diluent and drink to ensure total dose is taken. Always use the same diluent when giving the dose to minimize variation with drug absorption.
d. Or, for small children, simply measure the dose and squeeze directly into the mouth. May give small sips of fluid afterward to mask the taste.
e. Gtube administration: giving Neoral liquid by the Gtube is not an approved method of administration according to the pharmaceutical company, and they have not done any studies on this route or on the tubing. However, it is sometimes necessary to give Neoral liquid through a tube. 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 like apple or orange juice.
f. Milk should never be used to mix with Neoral Liquid, it is extremely unpalatable.

CAPSULES

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

8. CYCLOSPORINE DRUG INTERACTIONS

CsA is known to interact with many medications, and new interactions continue to be discovered as new medicines or herbal products are introduced.

CsA may interact with medications that increase its renal toxicity, or increase or decrease its blood levels, leading to toxicity or lack of effect.

Medications known to interact with cyclosporine are listed below. ***THIS LIST IS NOT COMPLETE!*** Be sure to check every medication, over the counter product, herbal, naturopathic or alternative medication for its safety with cyclosporine. [ref: Clinical Pharmacokinetics 1996; 30 (2): 141-79. Pharmacotherapy 1998; 18 (1): 84-112. Pharmacist's Letter 2006; 13 (2):220233]

Increased nephrotoxicity when combined with cyclosporine:

acyclovir	captopril	ganciclovir
aminoglycosides	ciprofloxacin	melphalan
amphotericin B	cotrimoxazole	NSAIDs

Enzyme (CYP 3A4) inhibitors

(increase CsA concentrations by decreasing metabolism)

amiodarone	erythromycin	ketaconazole
antiretrovirals	fluconazole	methylprednisolone
cimetidine	fluvoxamine	metronidazole
ciprofloxacin	grapefruit	miconazole
clarithromycin	isoniazid	nifedipine
contraceptives (oral)	itraconazole	voriconazole
diltiazem		

Enzyme (CPY 3A4) inducers

(decrease CsA concentrations by decreasing metabolism)

carbamazepine	oxcarbazepine	primidone
garlic supplements	phenobarbital	rifampin
octreotide	phenytoin	St. John's Wort

Increase Absorption of CsA

cisapride	erythromycin	metoclopramide

Decrease Absorption of CsA

Bowel cleansing preps (PEG with electrolytes, Go-Lytely and other brand names)	octreotide	phenytoin

Other

Digoxin concentrations may rise when taken with cyclosporine.

Caspofungin concentrations may be increased when given concurrently with cyclosporine; increasing risk of caspofungin-induced liver toxicity.