Cyclosporine

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- **INTRODUCTION**
- Cyclosporine is an immunosuppressant that is used for the prevention of graft-versus-host disease in hematopoietic stem cell transplantation patients,
- for the prevention of graft rejection in solid organ transplant patients,
- and for the treatment of psoriasis,
- rheumatoid arthritis and
- a variety of other autoimmune diseases.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- The therapeutic range of cyclosporine used by clinicians varies greatly according to the type of assay used to measure cyclosporine and whether blood or serum concentrations are determined by the clinical laboratory

TABLE 15-1 Cyclosporine Therapeutic Concentrations for Different Assay Techniques and Biologic Fluids

ASSAY	BIOLOGIC FLUID	THERAPEUTIC CONCENTRATIONS (ng/mL)
High pressure liquid chromatography (HPLC), monoclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or monoclonal radioimmunoassay (various manufacturers)	Blood	100–400
High pressure liquid chromatography (HPLC), monoclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or monoclonal radioimmunoassay (various manufacturers)	Plasma	50–150
Polyclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or polyclonal radioimmunoassay (various manufacturers)	Blood	200–800
Polyclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or polyclonal radioimmunoassay (various manufacturers)	Plasma	100–400

- Because cyclosporine is bound to red blood cells, blood concentrations are higher than simultaneously measured serum or plasma concentrations. High pressure liquid chromatography (HPLC) assay techniques are specific for cyclosporine measurement in blood, serum, or plasma.

- Since cyclosporine metabolites are excreted in the bile, liver transplant patients immediately after surgery can have very high cyclosporine metabolite concentrations in the blood, serum, and plasma because bile production has not begun yet in the newly transplanted organ.
- For the purposes of the pharmacokinetic calculations and problems, cyclosporine concentrations in the blood using the cyclosporine-specific high pressure liquid chromatography assay results will be used.

adverse effects of cyclosporine

- Nephrotoxicity.
- Hypertension, hyperlipidemia, tremor, hirsutism, and gingival hyperplasia

CLINICAL MONITORING PARAMETERS

- the signs and symptoms associated with graft-versus-host disease:

Hematopoietic stem cell transplantation

- These include a generalized maculopapular skin rash, diarrhea, abdominal pain, hyperbilirubinemia, and increased liver function tests

Patients with severe chronic graft-versus-host disease may have involvement of the skin, liver, eyes, mouth, esophagus, or other organs similar to what might be seen with systemic autoimmune diseases.

For renal transplant patients

- Increased serum creatinine, azotemia, hypertension, edema, weight gain secondary to fluid retention, graft tenderness, fever, and malaise, hypertension, proteinuria

For hepatic transplant patients

fever, lethargy, graft tenderness, increased white blood cell count, change in bile color or amount, hyperbilirubinemia, and increased liver function tests.

For heart transplant patients, acute rejection is accompanied by low-grade fever, malaise, heart failure (presence of S3 heart sound), or atrial arrhythmia

When cyclosporine concentration should be measured

- If a patient experiences signs or symptoms of graft-versus-host disease or organ rejection
- If a patient encounters a possible clinical problem that could be an adverse drug effect of cyclosporine therapy
- During the immediate post-transplantation phase

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Cyclosporine is almost completely eliminated by hepatic metabolism (>99%).
- There are more than 25 identified cyclosporine metabolites (inactive)
- Most of the metabolites are eliminated in the bile.
- Less than 1% of a cyclosporine dose is recovered as unchanged drug in the urine.
- There is a large amount of intrasubject variability in cyclosporine concentrations obtained on a day-to-day basis, even when the patient should be at steady state.

- After liver transplantation

Cyclosporine is a low-to-moderate hepatic extraction ratio drug with an average liver extraction ratio of ~30%.

Because of this, its hepatic clearance is influenced by unbound fraction in the blood (fB), intrinsic clearance (Cl'int), and liver blood flow (LBF).

- Cyclosporine binds primarily to erythrocytes and lipoproteins, yielding unbound fractions in the blood that are highly variable (1.4–12%).
- Erythrocyte concentrations vary in transplant patients, especially those who have received hematopoietic stem cell or kidney transplants. Lipoprotein concentrations also vary among patients, and hyperlipidemia is an adverse effect of cyclosporine

For adults, The overall mean for all transplant groups is
a clearance of 6 mL/min/kg,
a volume of distribution equal to 5 L/kg,
and a half-life of 10 hours

In children (≥16 years old)
Average clearance is higher (10 mL/min/kg)
and mean half-life is shorter (6 hours).

In patients with liver failure
Because the drug is primarily eliminated by hepatic metabolism, clearance is lower (3 mL/min/kg) and half-life prolonged (20 hours)

- Obesity does not influence cyclosporine pharmacokinetics, so doses should be based on ideal body weight for these individuals
- Renal failure does not change cyclosporine pharmacokinetics, and the drug is not significantly removed by hemodialysis or peritoneal dialysis.

DRUG INTERACTIONS

- 1. agents known to cause nephrotoxicity when administered by themselves

include aminoglycoside antibiotics, vancomycin, cotrimoxazole (trimethoprim-sulfamethoxazole), amphotericin B, and antiinflammatory drugs (azapropazone, diclofenac, naproxen, other nonsteroidal antiinflammatory drugs). Other agents are melphalan, ketoconazole, cimetidine, ranitidine, and tacrolimus.

2.involves inhibition or induction of cyclosporine metabolism.

Cyclosporine is metabolized by CYP3A4 and is a substrate for P-glycoprotein

Drugs that inhibit cyclosporine clearance include the calcium channel blockers (verapamil, diltiazem, nicardipine), azole antifungals (fluconazole, itraconazole, ketoconazole), macrolide antibiotics (erythromycin, clarithromycin), antivirals (indinavir, nelfinavir, ritonavir, saquinavir), steroids (methylprednisolone, oral contraceptives, androgens), psychotropic agents (fluvoxamine, nefazodone)

other agents (amiodarone, chloroquine, allopurinol, bromocriptine, metoclopramide, cimetidine, grapefruit juice). Inducing agents include other antibiotics (nafcillin, rifampin, rifabutin), anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), barbiturates, aminoglutethimide, troglitazone, octreotide, and ticlopidine.

- Cyclosporine can also change the clearance of other drugs via competitive inhibition of CYP3A4 and/or P-glycoprotein. Drugs that may experience decreased clearance and increased serum concentrations when given with cyclosporine include prednisolone, digoxin, calcium channel blockers (verapamil, diltiazem, bepridil, nifedipine , other dihydropyridine analogues, sildenafil), ergot alkaloids,simvastatin, and lovastatin.

INITIAL DOSAGE DETERMINATION METHODS

- *pharmacokinetic dosing method*
- *Literature-based recommended dosing*

The goal of initial dosing of cyclosporine is to compute the best dose possible for the patient in order to prevent graft rejection or graft versus host disease given their set of disease states and conditions that influence cyclosporine pharmacokinetics, while avoiding adverse drug reactions.

- $Css = [F(D/\tau)] / Cl$ or
- $D = (Css\ Cl\ \tau) / F$,
- where F is the bioavailability fraction for the oral dosage form (F averages 0.3 or 30% for most patient populations and oral dosage forms),
- D is the dose of cyclosporine in milligrams,
- Cl is cyclosporine clearance in liters per hour,
- and τ is the dosage interval in hours.

If the drug is to be given intravenously as intermittent infusions, the equivalent equation for that route of administration

- $Css = (D/\tau) / Cl$ or
- $D = Css \cdot Cl \cdot \tau$

If the drug is to be given as a continuous intravenous infusion, the equation for that method of administration

- $Css = ko/Cl$, or
- $ko = Css\ Cl$, where ko is the infusion rate.

- **Example 1** HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral cyclosporine dose designed to achieve a steady-state cyclosporine trough blood concentration equal to 250 ng/mL.
- Answer:
- $D = (Css\ Cl\ \tau) / F$
- F averages 0.3 or 30% for most patient populations and oral dosage forms
- Cl = 6 mL/min/kg .75 kg . (60 min/h / 1000 mL/L) = 27 L/h
- D= (250 µg/L . 27 L/h . 12 h) / (0.3 . 1000 µg/mg) = 270 mg, rounded to 300 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 . 10 h = 50 h, or ~2 days).

- **Example 2** Same patient as in example 1, except compute an initial dose using intravenous cyclosporine.
- answer
- A 12-hour dosage interval will be used for this patient. (Note: ng/mL= µg/L and this concentration was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 µg/mg is used to change the dose amount to milligrams.)
- $D = Css \cdot Cl \cdot \tau$
- (250 µg/L . 27 L/h . 12 h) / (1000 µg/mg) = 81 mg, rounded to 75 mg every 12 hours.

- If the cyclosporine dose is given as a continuous infusion instead of intermittent infusions,
- the dosage equation is ko = Css . Cl = (250 µg/L . 27 L/h) / (1000 µg/mg) = 6.8 mg/h, rounded to 7 mg/h.

- **Literature-Based Recommended Dosing**
- Generally speaking, initial oral doses of 8–18 mg/kg/d or intravenous doses of 3–6 mg/kg/d ,(1/3 the oral dose to account for ~30% oral bioavailability) are used and vary greatly from institution to institution.

Example 3 HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral cyclosporine dose designed to achieve a steady-state cyclosporine trough blood concentration within the therapeutic range.

Answer:

- *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*
- The cyclosporine oral dosage range for adult patients is 8–18 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (8 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial cyclosporine dose for this patient is 600 mg/d given as 300 mg every 12 hours

- : Dose = 8 mg/kg/d . 75 kg = 600 mg/d or 300 mg every 12 hours.
- Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 . 10 h = 50 h, or ~2 days) of treatment.

- **Example 4** Same patient as in example 3, except compute an initial dose using intravenous cyclosporine.
- **1.** *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*
- The cyclosporine intravenous dosage range for adult patients is 3–6 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (3 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial cyclosporine dose for this patient is 200 mg/d given as 100 mg every 12 hours: Dose = 3 mg/kg/d · 75 kg = 225 mg/d, rounded to 200 mg/d or 100 mg every 12 hours.

- If the cyclosporine dose is given as a continuous infusion instead of intermittent infusions, the infusion rate is ko = (3 mg/kg/d · 75 kg) / (24 h/d) = 9.4 mg/h, rounded to 9 mg/h.
- Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

USE OF CYCLOSPORINE CONCENTRATIONS TO ALTER DOSES

- *linear pharmacokinetics*. Sometimes, it is useful to compute cyclosporine pharmacokinetic constants for a patient and base dosage adjustments on these. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the cyclosporine dose.
- Another approach involves *area under the concentration-time curve (AUC)* and adjusting the cyclosporine dose to attain a target AUC.
- Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where concentrations are obtained at suboptimal times or the patient was not at steady state when concentrations were measured.

- **Linear Pharmacokinetics Method**
- Because cyclosporine follows linear, dose-proportional pharmacokinetics, steadystate concentrations change in proportion to dose according to the following equation:
- Dnew/Css,new = Dold/Css,old or Dnew = (Css,new/Css,old)Dold

- **Example 5A** LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current steady-state cyclosporine blood concentration equals 375 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.
- Answer
- The patient would be expected to achieve steady-state conditions after the second day (5 t1/2 = 5 .10 h = 50 h) of therapy.
- total daily dose = 400 mg/dose .2 doses/d = 800 mg/d
- Dnew = (Css,new/Css,old)Dold = (200 ng/mL / 375 ng/mL) 800 mg/d = 427 mg/d, rounded to 400 mg/d

Pharmacokinetic Parameter Method

- It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired cyclosporine concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady state cyclosporine concentration.

$Cl = [F(D/\tau)] / Css$

$(F = 0.3)$

- If cyclosporine is administered intravenously, it is not necessary to take bioavailability into account: $Cl = (D/\tau) / Css$

- **Example 7** LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current steady-state cyclosporine blood concentration equals 375 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.
- Answer
- $Cl = [F(D/\tau)] / Css = [0.3 . (400 mg/12 h) .1000 \mu g/mg] / (375 \mu g/L) = 26.7 L/h.$
- $D = (Css. Cl \ .\tau) / F = (200 \mu g/L . 26.7 L/h .12h) / (0.3 . 1000 \mu g/mg) = 214 mg$, rounded to 200 mg every 12 hours.

- If the patient in example 8 received cyclosporine as a continuous infusion at a rate of 6 mg/h, the equivalent clearance and dosage adjustment computations would be:
- Cl = ko/Css = (6 mg/h . 1000 µg/mg) / (215 µg/L) = 27.9 L/h
- ko = Css . Cl = (350 µg/L · 27.9 L/h) / (1000 µg/mg) = 9.8 mg/h, rounded to 10 mg/h

- **Area Under the Concentration-Time Curve Method**
- Some solid organ transplant centers believe that measurement or estimation of cyclosporine area under the concentration-time curve (AUC) is the best way to optimize cyclosporine therapy. While AUC can be measured using hourly postdose cyclosporine levels, studies have shown that there is a strong correlation between 3–4 cyclosporine concentrations and the total AUC
- using linear pharmacokinetics to achieve the target AUC: Dnew/AUCnew = Dold/AUCold or
- Dnew = (AUCnew/AUCold)Dold,

Thanks for Listening