Cyclosporine

- **Is a cyclic polypeptide with immunosupressent properties that is used for:**
- **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 .**
- **Whether blood or serum concentrations are determined by the clinical laboratory.**

Note Because cyclosporine is bound to red blood cells, blood concentrations are higher than simultaneously measured serum or plasma concentrations.

HPLC –BLOOD –100_ 400 ng/mL

HPLC–PLASMA –50_150 ng/mL

Polyclonal fluorescenes –blood–200_800 ng/mL

Polyclonal fluorescence–plasma–100_400 ng/mL

Basic Clinical Pharmacokinetic Parameters

- **Cyclosporine is almost completely eliminated by hepatic metabolism (>99%)**
- **There is a large amount of intrasubject variability in cyclosporine concentrations obtained on a day-to-day basis.**
- **Cyclosporine is a low-to-moderate hepatic ER drug with an average liver ER of ~30%. Because of this, its hepatic clearance isinfluenced by (fB), (Cl'int), (LBF).**

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETIC OF CYCLOSPORINE

- **For adult with normal liver function, CL is 6 mL/min/kg, volume of distribution equal to 5 L/kg, and a half-life of 10 hours.**
- **clearance is higher (10 mL/min/kg) and mean half-life is shorter (6 hours) in children (≤16 years old).**
- **Because the drug is primarily eliminated by hepatic metabolism, clearance is lower (3 mL/min/kg) and half- life prolonged (20 hours) in patients with liver failure.**

Initial Dosage Determination Methods

1. **Pharmacokinetics Dosing Method**
2. **Literature Recommended Method**

1. Pharmacokinetic Dosing Method

1. Clearance Estimate

A patient is categorized according to the disease states and conditions that are known to change cyclosporine clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance rate. For example, an **adult transplant patient** with normal liver function would be assigned a cyclosporine clearance rate equal to **6 mL/min/kg**, while a **pediatric transplant patient** with the same profile would be assumed to have a cyclosporine clearance of **10 mL/min/kg.**

2. SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

τ is 12 hr for adult IV injection

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

$D = (Css \cdot Cl \cdot \tau) / F$

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 is
- $Css = (D/\tau) / Cl$ 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 is
- $Css = k_o/Cl$, or
- $k_o = Css \cdot Cl$, where k_o is the infusion rate.

3. STEADY-STATE CONCENTRATION SELECTION

Although it is unlikely that steady state has been achieved, cyclosporine concentrations are usually obtained on a daily basis, even when dosage changes were made the previous day, owing to the critical nature of the therapeutic effect provided by the drug.

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.

1. Estimate clearance according to disease states and conditions present in the patient.

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 27 L/h: Cl = 6 mL/min/kg · 75 kg · (60 min/h / 1000 mL/L) = 27 L/h

2. *Compute dosage regimen.*

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 conver-sion was not required. Also, a conversion constant of **1000 μg/mg** is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is

$$D = (Css \cdot Cl \cdot \tau) / F = (250\ \mu g/L \cdot 27\ L/h \cdot 12\ h) / (0.3 \cdot 1000\ \mu g/mg) = 270\ mg$$

, rounded to 300 mg every 12 hours.

NOTE: 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 in ex1, except compute initial dosage using IV Cyclosporine.**

1. Estimate clearance according to disease states and conditions present in the patient.

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 27 L/h: Cl = 6 mL/min/kg · 75 kg · 60 min/h / 1000 mL/L) = 27 L/h.

2. Compute dosage regimen.

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 milligrams.) The dosage equation for intravenous cyclosporine is

D = Css · Cl · τ =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.

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).

2.Literature-Based Recommended Dosing

In general, the expected cyclosporine steady-state concentration used to compute these doses is dependent upon the type of transplanted tissue and the posttransplantation time line.

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**) .

For obese individuals (>30% over ideal body weight), ideal body weight should be used to compute initial doses.

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.

1. 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

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce cyclosporine concentrations that are expected or desirable.

Because of pharmacokinetic variability, the narrow therapeutic index of cyclosporine, and the severity of cyclosporine adverse side effects, measurement of cyclosporine concentrations is mandatory for patients to ensure that therapeutic, nontoxic levels are present. In addition to cyclosporine concentrations, important patient parameters (transplanted organ function tests or biopsies, clinical signs and symptoms of graft rejection or graft-versus-host disease, potential cyclosporine side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

For hematopoietic stem cell transplantation patients, steady-state trough concentrations are typically measured for cyclosporine. For solid organ transplant patients, the optimal times and strategies for measurement of steady-state concentrations are somewhat controversial.

1. **Linear Pharmacokinetics Method**

   Because cyclosporine follows linear, dose-proportional pharmacokinetics, steady-state concentrations change in proportion to dose according to the following equation:

   Dnew/Css,new = Dold/Css,old or Dnew = (Css,new/Css,old)Dold

   where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration.

   The Css can be either a steady-state trough concentration or a steady-state concentration measured 2 hours (+/−15 minutes) after a dose (C2). When **C2** levels are used, recommended concentrations vary according to **transplant type and posttransplant time**.

   The advantages of this method are that it **quick and simple**. The disadvantage is steady-state concentrations are required.

   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.

1. Compute new dose to achieve desired concentration.

The patient would be expected to achieve steady-state conditions after the second day 5 t1/2 = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (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

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h).

Note: Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Example 5B LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is 5 months post transplant and receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current C2 steady-state cyclosporine blood concentration equals 1500 ng/mL. Compute a cyclosporine dose that will provide a C2 steady-state concentration of 800 ng/mL. (Note: This is the same case as in example 5A in order to illustrate differences between trough and C2 level monitoring.)

1. Compute new dose to achieve desired concentration.

The patient would be expected to achieve steady-state conditions after the second day (5 t1/2 = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d): Dnew = (Css,new/Css,old)Dold = (800 ng/mL / 1500 ng/mL) 800 mg/d =427 mg/d, rounded to 400 mg/d

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time. A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h).

Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

<u>Example 6</u> FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 75 mg every 12 hours of intravenous cyclosporine. The current steady-state cyclosporine concentration equals 215 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of **350 ng/mL**.

1. Compute new dose to achieve desired concentration.

The patient recently received a liver transplantation and would be expected to have a longer cyclosporine half-life if the organ is not yet functioning at an optimal level (t1/2 =20 h). Because of this, it could take up to 4 days of consistent cyclosporine therapy to achieve steady-state conditions (5 t1/2 = 5 · 20 h = 100 h or ~4 d).

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose =75 mg/dose · 2 doses/d = 150 mg/d):

Dnew = (Css,new/Css,old)Dold = (350 ng/mL / 215 ng/mL) 150 mg/d

= 244 mg/d, rounded to 250 mg/d or 125 mg every 12 hours. A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life up to 20 hours, the cyclosporine steady-state concentration could be obtained anytime after the fourth day of dosing (5 half-lives = 5 · 20 h = 100 h or 4 days). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

2. If the patient in example 6 received cyclosporine as a continuous infusion at a rate of 6 mg/h, the equivalent dosage adjustment computation would be:

Dnew = (Css,new/Css,old)Dold = (350 ng/mL / 215 ng/mL) 6 mg/h

= 9.8 mg/h, rounded to 10 mg/h

2. <u>Pharmacokinetic Parameter Method</u>

The pharmacokinetic parameter method 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. Cyclosporine clearance can be measured using a single steady-state cyclosporine concentration and the following formula for orally administered drug:

Cl = [F(D/τ)] / Css,

where Cl is cyclosporine clearance in liters per hour, F is the bioavailability factor for cyclosporine (F = 0.3), τ is the dosage interval in hours, and Css is the cyclosporine steadystate concentration in nanograms per milliliter which also equals micrograms per liter.

If cyclosporine is administered intravenously, it is not necessary to take bioavailability into account: **Cl = (D/τ) / Css**, where Cl is cyclosporine clearance in liters per hour, τ is the dosage interval in hours, and Css is the cyclosporine steady-state concentration in nanograms per milliliter which also equals micrograms per liter.

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.

1. Compute pharmacokinetic parameters.The patient would be expected to achieve steady-state conditions after the second day .5 t1/2 = 5 · 10 h = 50 h or 2 days) of therapy. Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = [F(D/τ)] / Css = [0.3 · (400 mg/12 h) · 1000 μg/mg] / (375 μg/L) = 26.7 L/h.

Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

3. Compute cyclosporine dose.

Cyclosporine clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (200 μg/L. 26·7 L/h · 12h) / (0.3 · 1000 μg/mg) = 214 mg, rounded to 200 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Example 8 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 75 mg every 12 hours of intravenous cyclosporine. The current steady-state cyclosporine concentration equals 215 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 350 ng/mL.

1. Compute pharmacokinetic parameters.The patient recently received a liver transplantation and would be expected to have a longer cyclosporine half-life if the organ is not yet functioning at an optimal level (t1/2 =20 h). Because of this, it could take up to 4 days of consistent cyclosporine therapy to achieve steady-state conditions (5 t1/2 = 5 · 20 h = 100 h or ~4 d). Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = (D/τ) / Css = [(75 mg/12 h) · 1000 μg/mg] / (215 μg/L) = 29.1 L/h. (Note: μg/L =

mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. Compute cyclosporine dose.

Cyclosporine clearance is used to compute the new dose: D = Css · Cl · τ = (350 μg/L. 29·1 L/h · 12h) / 1000 μg/mg = 122 mg, rounded to 125 mg every 12 hours.A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life up 20 hours, the cyclosporine

steady-state concentration could be obtained anytime after the fourth day of dosing (5 half-lives = 5 · 20 h = 100 h or 4 days). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

If the patient in example 8 received cyclosporine as a continuous infusion at a rate of mg/h, the equivalent clearance and dosage adjustment computations would be:

$Cl = ko/Css = (6\ mg/h \cdot 1000\ \mu g/mg) / (215\ \mu g/L) = 27.9\ L/h$

$ko = Css \cdot Cl = (350\ \mu g/L \cdot 27.9\ L/h) / (1000\ \mu g/mg) = 9.8\ mg/h$, rounded to 10 mg/h