Therapeutic Drug Monitoring

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Immunosuppressants
Cyclosporine & Tacrolimus

Cyclosporine is a cyclic polypeptide calcineurin inhibitor with immunosuppressant properties.

- It is used for:
  - The prevention of graft-versus-host disease in hematopoietic stem cell transplantation patients.
  - The prevention of graft rejection in solid organ transplant patients.
  - The treatment of psoriasis, rheumatoid arthritis, and a variety of other autoimmune diseases.

What are the causes of doing TDM to cyclosporin?

- Narrow therapeutic index
- The severity of cyclosporine adverse side effects
- Variable pharmacokinetics and unpredictable absorption.

Therapeutic and toxic concentrations

The therapeutic range of cyclosporine varies greatly according to:

1. The type of assay used to measure cyclosporine

- High-pressure liquid chromatography (HPLC)
- Polyclonal immunoassays

2. Whether blood or serum concentrations are determined by the clinical laboratory.

Cyclosporine Therapeutic Concentrations for Different Assay Techniques and Biologic Fluids

Assay	Biologic Fluid	Therapeutic Concentrations (ng/mL)
High-pressure liquid chromatography (HPLC), monoclonal immunoassay	Blood	100-400
High-pressure liquid chromatography (HPLC), monoclonal immunoassay	Plasma	50-150
Polyclonal immunoassay	Blood	200-800
Polyclonal immunoassay	Plasma	100-400

- **Desired cyclosporine concentrations differ between** the various types of transplants, change with time during the post-transplantation phase, and are often determined by protocols specific to the transplantation service and institution.

Basic clinical pharmacokinetic parameters

- Cyclosporine is almost completely eliminated by **hepatic metabolism (>99%).**
- Less than 1% of a cyclosporine dose is recovered as unchanged drug in the urine.
- 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%).

Variability of cyclosporin concentrations

- There is a large amount of intrasubject variability in cyclosporine concentrations.

There are many reasons for this variability:

1. Cyclosporine has low water solubility, and its gastrointestinal absorption can be influenced by many variables.
    - To improve absorption rate and bioavailability for original dosage form (Sandimmune, Novartis), a microemulsion version of the drug (Neoral, Novartis) was marketed to help reduce absorption variability.

2. The fat content of meals.

- Food containing a large amount of fat enhances the absorption of cyclosporine.
- Oral cyclosporine solution is prepared with olive oil and alcohol to enhance the solubility of the drug.

3. In the absence of bile salts , the absorption of cyclosporine can be greatly decreased.

Dosage forms and strengths

1. **Capsules and solution** are available in **regular form** (25-mg and 100-mg capsules; 100-mg/mL solution).
2. **Capsules and solution** are available in **microemulsion form** (25-mg, 50-mg, and 100-mg capsules; 100-mg/mL solution).
3. **Injection** for intravenous administration is available at a concentration of 50 mg/mL.

EFFECTS OF DISEASE STATES AND CONDITIONS ON CYCLOSPORINE PHARMACOKINETICS AND DOSING

Disease state/condition	Clearance	Half life	Comment
Adults	6 mL/min/kg	10 hours	
Children (≤16 years old)	10 mL/min/kg	6 hours	
Liver failure	3 mL/min/kg	20 hours	**Because the drug is primarily eliminated by hepatic metabolism, clearance is lower and half-life prolonged in patients with liver failure**
Volume of distribution=5 L/Kg			

INITIAL DOSAGE DETERMINATION METHODS

1. **The *Pharmacokinetic Dosing method***
2. ***Literature-based recommended dosing***

Pharmacokinetic Dosing Method

- pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

Steps:

1- Clearance Estimate

- Adult, normal liver function **6 ml/min/kg**
- Pediatric, normal liver function **10 ml/min/kg**
- Liver failure **3 ml/min/kg**

✓ ***Conversion of Cl unit from mL/min to L/h by multiply Cl * 60/1000***

2- Selection of Appropriate Pharmacokinetic Model and Equations

Route of administration	Equations
Oral	$Css=[F(D/\tau)]/Cl$ **or** $D = (Css \bullet Cl \bullet \tau)/F$
Intermittent infusions	$Css = (D/\tau)/Cl$ **or** $D = Css \bullet Cl \bullet \tau$
Continuous intravenous infusion	$Css = ko/Cl$ **or** $ko = Css \bullet Cl$

- **Css** in ng/mL = µg/L **[Css /1000 = mg/L]**
- **F** is the bioavailability fraction for the oral dosage form (F averages 0.3 or 30% for most patient populations and oral dosage forms & F=1 for IV]
- **D** is the dose of cyclosporine in **mg**.
- **Cl** is cyclosporine clearance in **L/h** **[ml/min *60/1000 = L/h]**
- **τ** is the dosage interval in hours **[12h]**
- **ko** is the infusion rate (ko= D/τ)

✓ If patient obese use ideal body weight.

Literature-Based Recommended Dosing

- Initial oral doses of **8-18 mg/kg/d** or intravenous doses of **3-6 mg/kg/d** are used and vary greatly from institution to institution. ***[because dose calculated /d, you should divide by 2 to obtain a dose every 12 h]***
- For obese individuals, ideal body weight should be used to compute initial doses.
- Initial doses for children are **15 mg/kg/d** orally or **5-6 mg/kg/d** intravenously infused over 2-6 hours.

USE OF CYCLOSPORINE CONCENTRATIONS TO ALTER DOSES

- When cyclosporine concentrations are measured in patients and a dosage change is necessary, the following methods can be used:

1. *Linear pharmacokinetics method*
2. *Pharmacokinetic parameters method*

Linear Pharmacokinetics Method

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

$$\textbf{D new/Css new = D old/Css old}$$

Or

$$\textbf{D new = (Css new/Css old) D old}$$

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.

1-Actual Cyclosporine clearance

Route of administration	Equation
Oral	$Cl = [F(D/\tau)]/Css$
Intravenous	$Cl = (D/\tau)/Css$

- 2- Calculate new dose

Route of administration	Equations		
Oral	$Css=[F(D/\tau)]/Cl$	**or**	$D = (Css \bullet Cl \bullet \tau)/F$
Intermittent infusions	$Css = (D/\tau)/Cl$	**or**	$D = Css \bullet Cl \bullet \tau$
Continuous intravenous infusion	$Css = ko/Cl$	**or**	$ko = Css \bullet Cl$

Tacrolimus

- Macrolide compound with immunosuppressant actions, act by calcineurin inhibition.

Indications:

- Solid organ transplant; heart, liver, kidney.
- Graft-versus-host in hematopoietic stem cell transplant patients

THERAPEUTIC AND TOXIC CONCENTRATIONS

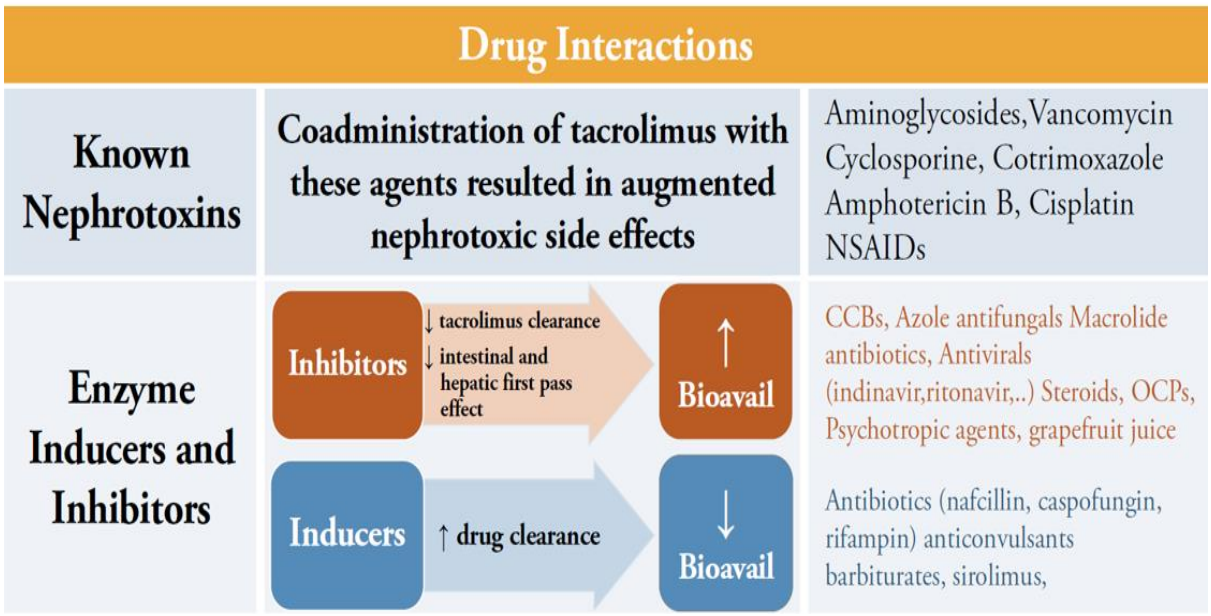
- The therapeutic range for tacrolimus used by most transplantation centers is **5-20 ng/mL** in blood.
- Although, plasma tacrolimus concentrations is (0.5-2 ng/mL), the most widely used assays for the drug use blood samples.

Organ	Desired Concentration	When to start therapy?	For how long?
Kidney	**5 -15ng/ml**	After kidneys begin functioning to avoid unwanted side effects on the new renal graft	Gradually tapered to the lowest concentration and dose possible over a 6-to 12-month time period as long as rejection episodes do not occur
Other Organs	**5 -20ng/ml**	Several hours **before** surgery	
Hematopoietic stem cell transplant		At the day of stem cell transplant (day 0) doses are adjusted to provide therapeutic trough concentrations	If successful(no or mild acute rejection episode) doses tapered on day 50, with the goal of drug discontinuation by day 180

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Absorption	Tmax0.5 –1hr Oral bioavailability ~25%
Distribution	binds primarily to erythrocytes, α1-acid glycoprotein, and albumin protein binding 72–99%
Metabolism	> 99% hepatic metabolism (CYP3A4) Active metabolites
Elimination	metabolites mostly eliminated in the bile < 1% unchanged in urine

EFFECTS OF DISEASE STATES AND CONDITIONS ON TACROLIMUS PHARMACOKINETICS AND DOSING	
Adult **Normal liver function**	Clearance: **0.06 L/h/kg** Volume of distribution: 1 L/kg Half-life: 12 h
Adult **Liver Dysfunction**	Clearance: **0.04L/h/kg** Volume of distribution: **3**L/kg Half-life: **60 h**(mean, range 28 –141 h)
Child **≤16 years**	Clearance: **0.138 L/h/kg** Volume of distribution: 2.6 L/kg Half-life: 12 h



Dosage forms and strengths

- Tacrolimus capsules are available in 0.5, 1, and 5 mg strengths.
- Tacrolimus injection for intravenous administration is available at a concentration of 5 mg/mL.

INITIAL DOSAGE DETERMINATION METHODS

1-The *Pharmacokinetic Dosing method*

2-Literature-based recommended dosing

Pharmacokinetic Dosing Method

- ***1- Clearance Estimate***

Disease state/condition	Tacrolimus Cl
Adult, normal liver function	0.06/L/h/kg
Child ≤16 years , normal liver function	0.138 L/h/kg
Liver dysfunction	0.04/L/h/kg

2- Selection of Appropriate Pharmacokinetic Model and Equations to calculate dose:

Route of administration	Equations
1. Oral	Css= [F(D/τ)]/Cl **or** D = (Css• Cl• τ)/F
2. continuous intravenous infusion	Css= ko/Cl **or** ko= Css• Cl

- **Css** in ng/mL = µg/L **[Css /1000 = mg/L]**
- ▪**F** is the bioavailability fraction for the oral dosage form (F averages 0.25 or 25% for most patient populations and oral dosage forms).
- ▪**D** is the dose of tacrolimus in mg.
- ▪**Cl** is tacrolimus clearance in L/h.
- ▪**τ** is the dosage interval in hours (τ for tacrolimus= 12 hr)
- ▪**ko** is the infusion rate.

STEADY-STATE CONCENTRATION SELECTION

- The generally accepted therapeutic range for tacrolimus in the blood is **5–20 ng/mL**.

Literature-Based Recommended Dosing

- Generally, initial oral doses of **0.1–0.3 mg/kg/d** are needed to achieve therapeutic tacrolimus steady-state concentrations.
- Usual initial continuous infusion intravenous doses are **0.03–0.1 mg/kg/d.**
- For patients with liver dysfunction, these doses may be reduced by **25–50%.**

USE OF TACROLIMUS CONCENTRATIONS TO ALTER DOSES

- •1. linear pharmacokinetics method
- •2. Pharmacokinetic parameters method

Linear Pharmacokinetics Method

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

  - **D new= (Css new/Css old) D old**

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 tacrolimus concentrations.
- Actual Tacrolimus clearance

Route of administration	Equation
oral	Cl= [F(D/τ)] / Css
intravenous	Cl= ko/Css

where Cl is tacrolimus clearance in **L/h**

- 2- Calculate new dose

Route of administration	Equations
1. Oral	D = (Css• Cl• τ)/F
2. continuous intravenous infusion	ko= Css• Cl