Cyclosporine

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Therapeutic and toxic concentrations

- The therapeutic range of cyclosporine used by clinicians **varies** greatly according to

    1. the type of assay used to measure cyclosporine.
    2. whether blood or serum concentrations are determined by the clinical laboratory.

Therapeutic and toxic concentrations

- High pressure liquid chromatography (HPLC) (Blood) 100-400 (ng/mL)
- High pressure liquid chromatography (HPLC) (Plasma) 50-150 (ng /mL)
- Polyclonal fluorescence polarization immunoassay (Blood) 200-800 (ng/mL)
- Polyclonal fluorescence polarization immunoassay (Plasma) 100-400 (ng/mL)
- Because **cyclosporine** is bound to **red blood cells**, blood concentrations are **higher** than simultaneously measured serum or plasma concentrations.

Basic Clinical Pharmacokinetic Parameters

- Cyclosporine is almost completely eliminated by hepatic metabolism (>99%).

- 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 (f_B)***
  - ***intrinsic clearance (Cl'_{int})***
  - ***liver blood flow (LBF)***

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Basic Clinical Pharmacokinetic Parameters

- There is a large amount of intrasubject variability in cyclosporine concentrations obtained on a day-to-day basis, even when the patient on steady state. There are many reasons for this variability.
  - ***Cyclosporine has low water solubility.***
  - ***Cyclosporine gastrointestinal absorption can be influenced by many variables.***

Basic Clinical Pharmacokinetic Parameters

- To improve the consistency of absorption rate and bioavailability for original dosage form (Sandimmune, Novartis), a micro emulsion version of the drug (Neoral, Novartis) was marketed to help reduce absorption variability.

- While use of micro-emulsion cyclosporine does decrease steady-state concentration variability

(10–30% for Neoral versus 16–38% for Sandimmune trough concentrations).

Basic Clinical Pharmacokinetic Parameters

- Cyclosporine capsules and solution are available in regular (25-mg, 50-mg, and 100-mg capsules; 100-mg/mL solution) and micro emulsion (25-mg and 100-mg capsules; 100-mg/mL solution) form.

- Cyclosporine injection for intravenous administration is available at a concentration of 50 mg/mL.

- Before administration, each milliliter of the concentrate should be diluted in 20-100 mL of normal saline or 5% dextrose, and the total dose infused over 2–6 hours.

Questions

Pharmacokinetically; what are the differences between the cyclosporine formulation (Sandimmune®) and the cyclosporine-modified formulations (Neoral®and Gengarf®)?

Answer

- The cyclosporine-modified formulations absorbed faster (i.e.; shorter T_{max}), to a greater extent (i.e.; higher AUC and C_{max}) and more consistently (i.e.; decreased intrapatient and interpatient variability).

- Therefore; they are not considered bioequivalent formulations and therefore should not be used interchangeably.

Questions

Why original cyclosporine formulation (Sandimmune®) is no longer commonly used?

Answer

- Because of its pharmacokinetic limitations and hence patients may receiving this brand if they are on a stable regimen and wish to continue with this particular formulation.

- Therefore; most patients who are initiated on a cyclosporine-based immunosuppression regimen are started with a cyclosporine-modified formulation.

Questions

What are the factors that are important in the determination of cyclosporine blood trough concentrations?

Answer

- ***organ(s) transplanted.***
- ***time after transplant.***
- ***transplant center-specific immunosuppression protocols.***

Clearance and Half-Life

For **adults**

Cl = 6 mL/min/kg

Half-life = 10 hours

For **children**

(≤16 years old) Cl = 10 mL/min/kg

Half-life = 6 hours

Patients with **liver failure**

Cl = 3 mL/min/kg

Half-life = 20 hours

Pharmacokinetics

- Vd = 5 L/kg

- 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.

Initial Dosage Determination Methods

1. **Pharmacokinetic Dosing Method**

2. **Literature-Based Recommended Dosing**

Pharmacokinetic Dosing Method

1. Clearance estimate

Clearance for adult…… ……..6 mL/min/kg.

Children (≤16 years old). ……. (10 mL/min/kg)

Patients with liver failure ……. (3 mL/min/kg)

2. Clearance should be converted to L/hr.

Clearance × weight (Kg) × 60 /1000

3. (Css in ng/mL converted to mg/L) by dividing the Css on 1000

Pharmacokinetic Dosing Method

4. Selection of pharmacokinetic equations

τ= 12 hr. for adult and I.V injection

F= 0.3

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

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

K_0= Css. CL …….for I.V infusion

Example

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:

1. **Estimate clearance**

The mean cyclosporine clearance for adult patients is 6 mL/min/kg.

$Cl = 6\ mL/min/kg \cdot 75\ kg \cdot (60\ min/h\ /\ 1000\ mL/L)$

$= 27\ L/h$

Example

2. <u>Compute dosage regimen.</u>

A 12-hour dosage interval will be used for this patient.

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.

Literature-Based Recommended Dosing

- Initial oral doses of 8–18 mg/kg/d
- Intravenous doses of 3–6 mg/kg/d
- For obese individuals (>30% over ideal body weight) ideal body weight should be used to compute initial doses.

Literature-Based Recommended Dosing

- Cyclosporine therapy is commonly started 4–12 hours before the transplantation procedure. According to a survey of transplant centers in the United States, the average initial oral dose (± standard deviation) for

renal transplant patients 9 ± 3mg/kg/d

liver transplant patients 8 ± 4mg/kg/d

Heart transplant patients 7 ± 3 mg/kg/d

- For both rheumatoid arthritis and psoriasis, the recommended initial dose is 2.5 mg/kg/d administered twice daily as divided doses with maximal recommended doses of 4 mg/kg/d.

Use of cyclosporine concentrations to alter doses

1. **Linear Pharmacokinetics Method**

2. **Pharmacokinetic Parameter Method**

Linear Pharmacokinetics Method

$$D_{new}/Css_{new} = D_{old}/Css,_{old}$$

$$D_{new} = (Css_{new}/Css_{old})D_{old}$$

- The steady state concentration used here either average C_{SS} or recent studies have found that the steady-state cyclosporine concentration 2 hours after a dose (C_2) reflects cyclosporine area under the curve better than an average concentration

Pharmacokinetic Parameter Method

- It allows the computation of an individual's own, unique pharmacokinetic constants (actual CL) and uses those to calculate a dose that achieves desired cyclosporine concentrations.

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

The resulted Cl will be in L/hr.

- Then compute cyclosporine dose by using actual Cl Cyclosporine clearance and desired Css

- The new dose:
  - $D = (Css \cdot Cl \cdot \tau) / F$


thank you!