Pharmacokinetics of Maintenance Immunosuppressive Drugs after Transplantation
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Guido Filler, MD, PhD, FRCPC
London, Canada

Pediatric Nephrology Seminar 2019
Disclosures

• I have no financial relationships to disclose relevant to my presentation
Objectives

• To understand why some drugs have highly variable drug exposure

• To learn about the concept of a narrow therapeutic window

• To learn about the risks of switching formulations of antirejection drugs

• Why patients should stay on the same formulation if stable?
Which statement is correct?

1. Tacrolimus drug levels are not affected by the methodology
2. There is no need for pharmacokinetic monitoring of Mycophenolate Mofetil (MMF) therapy
3. Immunosuppressive drug metabolites may be markedly different in children when compared to adults
4. Tacrolimus and MMF are considered critical dose drugs
1. The Basics
The Basics of Immunosuppressive Drugs

Combination of synergistic drugs main strategy to prevent rejection:

Therapeutic drug monitoring (TDM) mandatory for CNIs and mTOR inhibitors

TDM is favoured because of

- Large intraindividual variability
- Toxicity (which may be severe)
- Drug-to-drug interactions
Pharmacokinetics of Immunosuppressive Drugs

- 1983: Cyclosporin A (Sandimmune®)
  - Muromonab CD3 (Orthoclone OKT3®)

- 1986: Tacrolimus (Prograf®) for liver transplantation
  - Daclizumab (Zenapax®)

- 1994: Cyclosporine (Neoral®)
- 1995: Tacrolimus (Prograf®) for kidney transplantation
- 1997: Basiliximab (Simulect®)
- 1998: Sirolimus (Rapamune®)
- 1999: rTAG (Thymoglobulin®)
- 2010: Everolimus (Zortress®)

Medscape
In general transplant recipients receive therapeutic regimes

- All immunosuppressants are considered narrow therapeutic index drugs or “Critical Dose Drugs”

- Therapeutic drug monitoring is not enough to guarantee long term success

- Health Canada recognizes 9 Critical Dose Drugs including CNIs and mTOR inhibitors
Pharmacokinetic variability

1. Genetic

2. Variability due to disease (inflammatory bowel)

3. Age and body size

4. Concomitant drugs

5. Environmental factors (e.g. foods, pollutants, grapefruit juice)
Basis of drug variability

Drug variability

Nature Reviews | Drug Discovery

Western Medicine & Dentistry
Schulich School of Medicine & Dentistry
Basis of drug variability

Drug variability

Substrates

- Organic cations and weak organic bases with hydrophobic regions, some polypeptides, about half of commonly prescribed drugs
- Organic anions with hydrophobic regions (LTC4, vincristine, daunorubicin, etoposide, MTX, glutathione, glucuronide, and sulfate conjugates), HIV-protease inhibitors
- Cyclic nucleotides and derivatives (PMEA), some organic anions and weak organic acids (MTX)
- Organic cations and weak organic bases with hydrophobic regions, some anionic drugs (MTX, topotecan, mitoxantrone)

TRENDS in Pharmacological Sciences
Drug Metabolizing Enzymes

Drug Dosing
The Specifics of Drug Metabolism in the Growing Body

Example: Changes in the metabolic capacity of the UGTs explain why the MMF dose has to be higher in young children compared with adolescents, as less MPA-G is formed and therefore less recirculation.

Therapeutic Drug Monitoring to accommodate inter- and intra-patient variability
Narrow therapeutic window

Therapeutic window:

Definition:
The range of dosage of a drug or of its concentration in a bodily system that provides safe effective therapy.

A usually short time interval (as after a precipitating event) during which a particular therapy can be given safely and effectively.
Narrow therapeutic range drugs
The effect of polymorphisms on drug metabolism

Therapeutic window

Drug Metabolism (Degradation)

Drug Receptor (Efficacy)

<table>
<thead>
<tr>
<th>Metabolism genotype</th>
<th>Receptor genotype</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Efficacy</td>
</tr>
<tr>
<td>65%</td>
<td>Low (5%)</td>
<td></td>
</tr>
<tr>
<td>32%</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>79%</td>
<td>Moderate (15%)</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>High (80%)</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

Polygenic Drug Response

Western Medicine & Dentistry
Schulich School of Medicine & Dentistry
Why Therapeutic Drug Monitoring (TDM)?

• Drug dosing is based on the assumption that a certain dose yields a certain concentration in the body fluids.

• Optimum concentration: ineffectively low $<$ target level $<$ toxicity

- therapeutic window -

• Variability
  – Inter-patient
  – Intra-patient
  – Drug interactions caused by concomitant medication
Therapeutic Drug Monitoring

• A more appropriate description for the optimum use of drug concentration in clinical practice is TARGET CONCENTRATION INTERVENTION

• Surrogate effect—a convenient substitute for the desired therapeutic outcome

• Intervention in dose adjustment to achieve target drug concentration lowers variation in dose response relationship
Targeting Cyclosporine exposure in children

Pharmacokinetics of Immunosuppressive Drugs

Target Cyclosporin exposure in children

Target Cyclosporin exposure in children

Fig. 3 Incidence of rejection episodes after the first 100 days and proportion of histologically confirmed chronic CyA toxicity in relationship to AUC. Total numbers of observations are plotted above columns.

Concept of TDM

• Based on the fact that there is a definable relationship between dose, plasma concentration, and therapeutic effect
Clinical usefulness of TDM

• Maximize efficacy of drug
• Avoiding toxicity
• Identifying therapeutic failure
• Facilitating dose adjustment
• Facilitating therapeutic effects
When is TDM required?

- Critical minimal concentration required – **Examples:** antibiotics, oral ganciclovir, anti-rejection drugs
- Considerable **toxicity** - **Example:** Aminoglycosides (Gentamycin), Vancomycin, Methotrexate etc.
- Narrow therapeutic window – **Example:** Cyclosporine, Tacrolimus
- Substantial **interindividual variability** – **Example:** Cyclosporine
- **Intraindividual variability** due to alterations in metabolism – **Example:** Tachyphylaxy
- **Drug interactions** – **Example:** INH or Macrolides on Cyclosporine
Pharmacokinetic Profiles vs. Limited Sampling Strategies
Changes in drug absorbed

AUC changes, $C_{\text{max}}$ also changes

Pharmacokinetics of Immunosuppressive Drugs

Tacrolimus PK Profiles

![Graph showing Tacrolimus PK Profiles](image-url)
Tacrolimus: Correlation between AUC and C0

Pharmacokinetics of Immunosuppressive Drugs

AUC [ng x h/ml]

Tacrolimus trough conc. [ng/ml]

$r^2 = 0.5245$

$p < 0.0001$
MPA PK Profiles in 104 Paediatric Renal Transplant Recipients

N=104 renal transplant patients
Lack of Correlation between MPA Dose and MPA AUC

Pharmacokinetics of Immunosuppressive Drugs
Correlation between MPA AUC and Abbreviated AUC from C1, 2 and 6

\[ 10.75 + 0.98 \cdot C_1 + 2.38 \cdot C_2 + 4.86 \cdot C_6 \]

\[ r^2 = 0.8390 \]

Dose-normalized AUC Varies with Concomitant Medication

Dose normalized mean MPA concentration (µg·m²/ml·mg)

Time after oral intake (h)

None
CyA
Tac

Is the Trough Level So Bad if Only Concomitant Tac is Considered?

MPA and C0 correlation

MPA trough level [ug/ml]

MPA AUC [mg x h/L]
What to use for which drug?

- Old Sandimmune® - $C_0$
- Cyclosporine Neoral® - $C_2$?
- Tacrolimus - $C_0$
- MMF – LLS ($C_0$ if with concomitant Tacrolimus)
- Sirolimus – $C_0$
Drug Interactions
CNIs – known drug interactions

Table 3. Effect of various drugs on tacrolimus metabolism by human liver microsomes

<table>
<thead>
<tr>
<th>Inhibition (%)</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>Ketoconazole*</td>
</tr>
<tr>
<td>70–61</td>
<td>Cyclosporin A, nifedipine</td>
</tr>
<tr>
<td>50–41</td>
<td>Diltiazem, ethinyl estradiol, nilvadipine</td>
</tr>
<tr>
<td>40–31</td>
<td>Astemizole, erythromycin, prednisolone, terfenadine</td>
</tr>
<tr>
<td>30–21</td>
<td>Fluconazole, rifampicin</td>
</tr>
<tr>
<td>20–10</td>
<td>Amphotericin B, cefixime, ciprofloxacin, licomycin, norethindrone, ofloxacin, omeprazole, quinidine, sulindac</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Acyclovir, azulene, cefalexine, cefotaxime, chlorpheniramine, cimetidine, clemastine, cycroheptadine, diclofenac, enoxacin, etizolam, fosfomycin, gentamycin**, homochlorcyclizine, hydroxyzine, indomethacin, kanamycin, ketotifen, loxoprofen, minocycline, phenobarbital, phenylbutazon, promethazine</td>
</tr>
</tbody>
</table>

Underlined drugs: clinically relevant drug interactions with tacrolimus were reported.*

Concentrations of tacrolimus and drugs were 10 and 100 μM, respectively.

*: Concentration of ketoconazole was 10 μM.

**: Concentration of gentamycin was 60 μg/mL.
## Drug interactions with cyclosporine and tacrolimus

<table>
<thead>
<tr>
<th>Increase CNI levels</th>
<th>Decrease CNI levels</th>
<th>Increase CNI nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, Fluconazole</td>
<td>Anticonvulsants: Phenytoin, phenobarbital, carbamazepine, others</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Erythromycin and other macrolides</td>
<td>Antibiotics, rifampicin, rifabutin</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Diltiazem, Verapamil, Nicardipine</td>
<td>NSAIDS</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Methylprednisolone</td>
<td></td>
</tr>
<tr>
<td>Sirolimus (CyA only)</td>
<td>Sirolimus + Tacrolimus level &gt; 15 (ng/mL)²</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice, St. John’s wart, Schisandra extract</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CNIs – known drug interactions

Pharmacokinetics of Immunosuppressive Drugs

[Diagram showing drug interactions and transport mechanisms across different body compartments (GL Lumen, Enterocyte, Blood, Hepatocyte, Blood, Kidney PT Cell, Urine)]

- Tacrolimus metabolism by CYP3A4/5
- M-1 metabolism by CYP3A4/5
- M-VII metabolism by CYP3A4/5
# Metabolism Pathways

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>CYP3A4, CYP3A5, CYP2D6</td>
<td>CYP3A4 – intestinal, CYP3A5, P-gp</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>CYP3A4 (moderate), UGT1A1, P-gp</td>
<td>CPY3A4, P-gp</td>
</tr>
<tr>
<td>Inducer</td>
<td>NONE</td>
<td>NONE</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Methylprednisolone</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetics of Immunosuppressive Drugs
## Pharmacokinetics of Immunosuppressive Drugs

### Drug interactions with mTOR inhibitors

<table>
<thead>
<tr>
<th>Increase mTOR levels</th>
<th>Decrease mTOR levels</th>
<th>Increase nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotrimazole, Voriconazole</td>
<td>Anticonvulsants: Phenytoin, phenobarbital, carbamazepine, others</td>
<td></td>
</tr>
<tr>
<td>Danazole, Cimetidine, Metoclopramide, Bromocriptine, Protease inhibitors, Nicardipine, Cisapride, Verapamil</td>
<td>Antibiotics, rifampicin, Rifabutin</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Cholestyramine</td>
<td></td>
</tr>
<tr>
<td>Ritanovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td>Concomitant Tacrolimus, combined level &gt; 15 ng/mL</td>
</tr>
</tbody>
</table>
### Drug interactions with MMF/MPA

<table>
<thead>
<tr>
<th>Antimetabolites MMF/MPA</th>
<th>Cyclosporine</th>
<th>Aciclovir</th>
<th>Ganciclovir</th>
<th>Antacids</th>
<th>Proton pump inhibitors</th>
<th>Ca-free PO4 binders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in MPA AUC</td>
<td>Possible increase in AUC</td>
<td>Decreased clearance of Ganciclovir</td>
<td>Decrease in AUC and Cmax</td>
<td>MMF decrease in Cmax and Tmax, no effect on MPA</td>
<td>Decrease in AUC and Cmax</td>
<td>Decrease in AUC and Cmax</td>
</tr>
<tr>
<td>Dose adjustment may be necessary</td>
<td>Monitor for adverse effects</td>
<td>Monitor for adverse effects of ganciclovir levels</td>
<td>Avoid</td>
<td>Caution with MMF</td>
<td>Administer 2 h after MMF</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• There are multiple drug interactions, not only at the level of the enzymes (particularly CYP3A4 and CYP3A5), but also at the level of transporter proteins, especially P-gps (MRP2).
• Knowledge of the drug disposition of drugs you want to co-administer is helpful in predicting drug interactions.
• The multi-drug approach that we choose is so complex that monitoring of all critical dose drugs and MPA is recommended, and AUC testing (limited sampling strategies) is better than trough level testing alone.
Examples of ontogeny
Age dependency of dose required for an AUC of 60 ug x h/mL in children on Tacrolimus and Mycophenolate Mofetil (MMF)

## ANOVA/Kruskal Wallis Results

<table>
<thead>
<tr>
<th></th>
<th>n = 37</th>
<th>&lt;6 years</th>
<th>6–12 years</th>
<th>&gt;12 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Normalized MPA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trough levels [mg/kg]</td>
<td>0.0526</td>
<td>0.110</td>
<td>0.134</td>
<td></td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(0.0882-0.286)</td>
<td>(0.0705-0.157)</td>
<td>(0.0692-0.226)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose Normalized MPA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trough levels [mg/m²]</td>
<td>2.195 x 10⁻³</td>
<td>3.775 x 10⁻³</td>
<td>3.997 x 10⁻³</td>
<td></td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(1.040-3.438 x 10⁻³)</td>
<td>(2.505-5.533 x 10⁻³)</td>
<td>(2.228-6.510 x 10⁻³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Steroid Dose/day [mg/kg]</strong></td>
<td>0.203</td>
<td>0.112</td>
<td>0.147</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(0.0882-0.286)</td>
<td>(0.0622-0.190)</td>
<td>(0.0675-0.238)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematocrit [%]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>Mean (±1 SD)</td>
<td>30.58 (±5.12)</td>
<td>34.91 (±4.16)</td>
<td>32.34 (±5.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Albumin [g/L]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>41.0</td>
<td>41.0</td>
<td>43.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(36.0-43.0)</td>
<td>(38.0-44.0)</td>
<td>(40.0-45.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR [mL/min/1.73 m²]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>70.50</td>
<td>76.0</td>
<td>67.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(18.75-88.0)</td>
<td>(67.0-88.0)</td>
<td>(41.0-87.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Yoo E. et al. Pediatr Nephrol. 2016 Jun;31(6):975-82*
Key fragmentation pathways of Sirolimus/Everolimus used for identification of metabolites. Fragment structure were identified by analysis of MS\(^3\), high resolution ESI sectorfield MS and comparison of Sirolimus derivatives.
Main metabolism positions of sirolimus

Group 1
CYP 3A4/3A5

Group 2
CYP 3A5/3A4

Group 3
CYP 2C8/3A4/3A5

Group 4
CYP 3A4

= Demethylation
= Hydroxylation
Sirolimus metabolites identified

- Known metabolites found in adults were not detected:
  - 11-hydroxy Sir
  - 25-hydroxy Sir
  - Di-demethylated Sir
- 77.5% of the metabolites were hydroxylated metabolites
- Major metabolite in adults, 39-O-desmethyl Sir, accounted for only 8.4%.
- 16-O-desmethyl Sir was the major demethylated metabolite detected
- Proportion of Piperidine-hydroxy Sir correlated significantly with age
Discussion of *in vivo* Sir metabolite results

- 39-O-desmethyl Sir accounted for only 8.4%.
- 16-O-Desmethyl Sir was the major demethylated metabolite detected.

This is of clinical importance since 39-O-desmethyl Sir is reported to show 86-127% cross-reactivity with the Sir immunoassay.

- Immunoassay users: Do we need lower target AUCs in children?
- Overall, there was large inter-individual variability in the metabolite patterns.
- Metabolites reached a median AUC of 60% of that of Sir, but the range was 2.6-136%.
Summary

• Therapeutic Drug Monitoring (TDM) is required for calcineurin inhibitors and mTOR inhibitors
• There is growing evidence for the need of TDM of MMF therapy
• As a transplant nephrologist, you need to know your target exposure and the best tool for monitoring (trough level or LSS)
• Ontogeny of drug disposition is very complex
• Drug interactions, developmental changes and many other reasons are making a prediction of exposure difficult and their knowledge cannot replace the need for TDM.