Transplant Medications: Review of Interactions

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Nurse Practitioners Symposium
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Objectives

1.) Discuss the CYP450 enzymes and other mechanisms of drug interactions

2.) Identify pertinent drug-drug interactions in transplant patients

3.) Recommend dose adjustments and/or alternative therapies when appropriate

4.) Review patient case
Just a reminder….

• This talk will *not* cover a complete list of drug interactions

• Highlighting those interactions that are most often encountered in daily practice

• Evidence for a stepwise approach for the management of drug interactions is not always available
  – Often you will need to work within center protocols and trust experience (or ask your pharmacist)
Quick History Review

- Drug interactions reported in the literature since the beginning of cyclosporine utilization
  - 1986: Erythromycin and cyclosporine
  - Early 1990’s: Ketoconazole and cyclosporine
  - 1993: Grapefruit interaction with cyclosporine

- A book called “Drug Interactions” went to press 35yrs ago and contained a few hundred drug interactions
  - Today, the book is called “Drug Interactions Analysis and Management” and contains thousands of interactions

Growing Problem…

• The likelihood of a drug interaction increases with the number of medications a patient is taking
  – Polypharmacy is an everyday part of a transplant patients regimen

• Interactions are unavoidable for transplant patients
  – Routinely use medications that interact
  – Occasionally, medications are used because of their interaction
  – Newly approved medications can present a problem
What is your opinion?

A.) I never see drug interactions in my transplant patients

B.) I dislike drug interactions and hope that I don’t have to deal with them much or at all

C.) I am good at managing the main interactions, the new drugs/less well known interactions make me nervous

D.) I let my transplant pharmacist deal with interactions….that’s their job, after all
Why Focus on Drug Interactions?

- Low Levels
- High Levels
- Side Effects
- Rejection
- Malignancies
Factors That Contribute to Drug Interactions

• Time course of drug interactions
  – Important for monitoring of levels

• Determinants of time course
  – Half lives of drugs
  – Drug dosage
  – Route of administration
  – Metabolites
  – Pharmacodynamics
  – Pharmacokinetics
  – Enzyme Interactions
  – Genetics
  – Plasma protein binding

Wallemacq P, et al. Ther Drug Monit 2009; 31:139-153
Factors That Contribute to CNI Drug Interactions

- Unpredictability in exposure of CNIs occurs during the absorption/metabolism in the gastrointestinal tract
  - Site of absorption
    - Small intestine is the primary site
  - Rate and extent of absorption
  - Drug binding in the GI tract
  - Alterations in GI motility/pH
  - Intestinal flora

Wallemacq P, et al. Ther Drug Monit 2009; 31:139-153

CNI= Calcineurin Inhibitor
Drug interactions: CYP Enzymes

Proportion of Drugs Metabolized by P450 Enzymes

- CYP2D6: 19%
- CYP1A/2: 11%
- CYP2C19: 8%
- CYP2C8/9: 16%
- CYP2B6: 4%
- CYP2A6: 3%
- CYP3A4/5: 36%

What are the CYP 3A4 enzymes?

• CYP stands for Cytochrome
  – Membrane associated proteins

• Family 3, subfamily A, polypeptide 4

• CYP enzymes are found predominantly in the liver and aid in the metabolism of drugs
  – Estimated that CYP3A4 metabolizes about half of all drugs on the market
  – Metabolize thousands of endogenous and exogenous chemicals

What are Inducers?

- **INDUCER**: Increases the number of enzymes available for metabolism
  - May increase the metabolism of substrates
  - Leads to a decreased drug effect

## CYP450 3A4 Inducers

**Inducers DECREASE Tacrolimus/Cyclosporine Levels**

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Anti-tuberculosis Agents</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Rifampin</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Rifabutin</td>
<td>St. Johns Wart</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Isoniazid</td>
<td>Sirolimus (FK)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspofungin (FK)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What are Inhibitors?

- **INHIBITOR**: Decreases the activity of the enzyme
  - May decrease the metabolism of substrates
  - Competition for enzyme binding site
  - Leads to an increased drug effect
CYP450 3A4 Inhibitors

**Inhibitors INCREASE Tacrolimus/Cyclosporine Levels**

- **Calcium Channel Blockers**
  - Diltiazem
  - Verapamil
  - Nicardipine

- **“Azole” Antifungals**
  - Fluconazole
  - Itraconazole
  - Ketoconazole
  - Posaconazole
  - Voriconazole

- **“Mycin” Antibiotics**
  - Erythromycin
  - Clarithromycin

- **Anti-arrhythmic Agent**
  - Amiodarone

- **Immunosuppressive Agents**
  - Sirolimus (CyA)

- **Protease Inhibitors**
  - Saquinavir
  - Indinavir
  - Nelfinavir
  - Ritonavir

- **Food**
  - Grapefruit
  - Blood Oranges
  - Pomegranate?
P-glycoprotein (P-gp)

- Expressed in certain cell types in the liver, pancreas, kidney, colon, and jejunum
  - Cell membrane-associated protein that transports a variety of drug substrates

- Immunosuppressants are substrates of P-gp
  - Substrates get transported back to intestinal lumen as they are absorbed
Why is Tacrolimus So Difficult to Control?

**High PK variability**
- Interpatient variability
- Over- or underexposure can occur within the “therapeutic range”
  - TDM doesn’t help estimate the magnitude of drug interactions
- Low bioavailability
  - ~25% (4-89%)

**The gut**
- CNIs are lipophilic and diffuse easily into enterocytes
  - Forced back into intestinal lumen by P-gp
  - Metabolism by CYP3A4
  - Diffusion into portal circulation
- Each pass through the enterocytes can cause repeated metabolism via 3A4

<table>
<thead>
<tr>
<th>Effect</th>
<th>Tacrolimus</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor of CYP3A4</td>
<td>Weak</td>
<td>Strong</td>
</tr>
<tr>
<td>Inhibitor of P-gp</td>
<td>Weak</td>
<td>Strong</td>
</tr>
<tr>
<td>Effect of food</td>
<td>↓ AUC by 25-45%</td>
<td>Variable</td>
</tr>
<tr>
<td>Effect of diarrhea</td>
<td>↑ Bioavailability</td>
<td>No clear effect with Neoral</td>
</tr>
<tr>
<td>Effect of anemia</td>
<td>↑ Hepatic blood clearance</td>
<td>None</td>
</tr>
<tr>
<td>“Maturation” potential</td>
<td>Clearance decreases over time</td>
<td>Clearance does not appear to decrease over time</td>
</tr>
</tbody>
</table>


What does Tacrolimus want?!
Individual Drug Interactions
AZOLE Antifungals

• Isavuconazole (Cresemba)
• Voriconazole (Vfend)
• Posaconazole (Noxafil)
• Itraconazole (Sporanox)
• Ketoconazole (Nizoral)
• Fluconazole (Diflucan)
Isavuconazole: Points to Consider

• Broad spectrum azole antifungal approved in March 2015
  – Invasive Aspergillosis and Mucormycosis

• Moderate inhibitor of CYP3A4 and substrate
  – Long $t_{1/2} \sim 130$ hours
  – “Tacrolimus Use with Caution: Concomitant administration of CRESEMBA and tacrolimus results in an increase of tacrolimus exposure. Monitor drug concentrations of tacrolimus and adjust dose as needed”
Isavuconazole: Points to Consider

• Case report of a 30 yr old female s/p BOLTx in 2013
  – Pt diagnosed with *A. fumigatus* but poorly tolerated IV amphotericin therapy
  – Isavuconazole initiated at 200mg three times daily followed by 200mg once daily

• Tacrolimus dose cut by 43%
  – FK 3.5mg q12h → 2mg q12h
Authors Recommendations

• Suggest an initial 50% reduction in tacrolimus dose
  – Weekly monitoring of FK levels
  – Further dose decreased of 25-50% may be required over an 8 week period

Voriconazole: Points to Consider

- Second generation triazole antifungal agent
  - Activity against *Candida*, *Aspergillus* spp, *Cryptococcus neoformans* and *Fusarium* spp

- Bioavailability is ~90%
  - Rapid and complete absorption
  - Absorption not affected by antacids

- Half-life
  - Variable and dose dependent but ~6 hours

- Therapeutic Drug Monitoring should be considered

Theuretzbacher, U et al. *Clin Pharmacokinет* 2006; 45 (7) 649-663
Posaconazole Suspension: Points to Consider

• Extended coverage including *Zygomycetes*

• Food significantly increases the bioavailability
  – High fat meals had best systemic exposure
    • Should always be administered with meals
  – Sub-therapeutic levels noted in patients on concomitant PPI/H₂ blocker therapy

Posaconazole tablets: Points to Consider

- Delayed release, gastro-resistant film-coated tabs
  - pH sensitive polymer stabilizer that limits release of drug in the stomach
    - Posaconazole is released at more neutral small intestine pH
  - Administration is only moderately affected by food
    - Exposure ~35% higher with tabs when given with food
  - Exposure not affected by PPI/H₂ blockers

Posaconazole TDM

Start Prophylaxis/Treatment

Check a level after 7 days of therapy:
- Goal level is 1.25mg/L for treatment
- Goal level is 0.7mg/L for prophylaxis

A repeat level should be checked when:
- Negative clinical outcome
- Start/stop P-gp inhibitors/inducers
- Changing from tabs to susp

TDM = Therapeutic Drug Monitoring
Itraconazole: Points to Consider

**SOLUTION**

- Bioavailability is ~55%
- Absorption of solution is not affected by gastric pH
- Optimal absorption is on an empty stomach

**CAPSULES**

- Bioavailability is ~20%
- Absorption of capsules is enhanced by food and an acidic beverage
- Absorption of capsules is decreased when given with antacids

Fluconazole: Points to Consider

- Use is limited by narrow fungal coverage
  - Active against Candida species
    - Except *C. Krusei* and *C. glabrata*

- Undergoes little CYP-mediated metabolism
  - Less potent inhibitor than itra/vori
  - Doses of >200mg may be enough to inhibit CYP3A4 substrate clearance

What does all of this mean?
Vori/Itra and Tacrolimus Drug Interaction

• Most of the current data in lung and/or heart recipients
  – Case reports or retrospective data

• Kramer, et al. conducted a retrospective review of 60 lung tx pts
  – Tacrolimus dose reduction of 76% during itraconazole treatment and 64% during voriconazole treatment

• Capone, et al. noted the drug-drug interaction occurred within 2 days of starting itraconazole

Voriconazole and Sirolimus Drug Interaction

• Combination is not suggested per manufacturer recommendations

• Francisco et al, noted a 90% reduction was necessary
  – Achieved goal through sirolimus levels without toxicity

• Case reports in 2 renal transplant recipients
  – Dose reductions of 75% and 87% were necessary to avoid toxic sirolimus levels

## Immunosuppressant Dose Reductions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tacrolimus</th>
<th>Cyclosporine</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>40%</td>
<td>40%</td>
<td>50-70%</td>
</tr>
<tr>
<td>(Doses &gt;200mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>75-80%</td>
<td>~0-30%</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>50-60%</td>
<td>50-60%</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>66%</td>
<td>50%</td>
<td>90%**</td>
</tr>
</tbody>
</table>

**Combination is not recommended per manufacturer recommendations**

Individual Drug Interactions
Colchicine and Calcineurin Inhibitors

• In 2009, the FDA reported 169 deaths related to colchicine
  – 51% of the cases, patients were on concomitant clarithromycin therapy
  – Colchicine toxicities include:
    • Polyneuropathy
    • Myopathy
    • Rhabdomyolysis
    • Neutropenia
    • Heart Failure

Food and Drug Administration: Information for healthcare professionals: new safety information for colchicine; 2009.
Colchicine and Calcineurin Inhibitors

• Metabolism of colchicine is via 3A4
  – P-gp substrate
  – Chronic renal insufficiency

• Other studies suggest a 66% decrease in colchicine dose when administered with a CYP3A4 or P-gp inhibitor
  – Concentration can be 3 to 4 fold higher when given with cyclosporine

Severe Colchicine Intoxication in a Renal Transplant Recipient on Cyclosporine

Dosing Recommendations of the Authors

**Acute Gout Flare**

- Give 0.6mg once, dose can be repeated in 3 days

**Prophylaxis of Gout Flare**

- 0.3mg once daily or every other day


Myopathy and possible intestinal dysfunction in a patient treated with colchicine and simvastatin.

Oh DH, Chan SQ, Wilson AM.

PMID: 22994827
[PubMed - indexed for MEDLINE]

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Colchicine-Induced Rhabdomyolysis in a Heart/Lung Transplant Patient With Concurrent Use of Cyclosporin, Pravastatin, and Azithromycin

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Abstract: We report a case of colchicine-induced rhabdomyolysis in a heart/lung–transplanted man treated with cyclosporin. A treatment was
Colchicine and Statins

• Myopathy/rhabomyolysis has been described with colchicine and:
  – Simvastatin
  – Pravastatin
  – Fluvastatin
  – Atorvastatin

• P-gp inhibition by both colchicine and statins
  – Accumulation of metabolites

I’m not convinced we’ve wasted enough time on this.
Individual Drug Interactions
Statin Therapy and CNIs

• Cardiovascular disease is the leading cause of death in patients with a functioning renal transplant
  – Cardiovascular risk factors increased post transplant
    • Hypertension
    • Diabetes
    • Dyslipidemia

• More than 50% of renal transplant recipients are treated with statins
  – Good data to support the use of statins in this population

Statin Therapy and CNIs

- Literature demonstrates a long term benefit of statin therapy in heart transplant recipients
  - Beneficial effect on survival
  - Reduces the development of CAV
  - Wenke et al. note CAV in 18% of simvastatin treated patients vs. 42% of non-statin treated patients after a 4 year study period


Statin Therapy and CNIs

- “Atorvastatin AUC was significantly increased with concomitant administration of Lipitor 10 mg and cyclosporine 5.2 mg/kg/day compared to that of Lipitor alone.”
  - Patients taking 10 mg of atorvastatin with cyclosporine for 28 days showed 8.7-fold increase in atorvastatin AUC.

- “The co-administration of Lipitor with cyclosporine should be avoided.”

- “The combined use of simvastatin with cyclosporine significantly increased cyclosporine exposure. Co-administration of cyclosporine with LIVALO is contraindicated.”

## Statin Therapy with CNIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Avoid use</td>
<td>No dose adjustments mentioned</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Contraindicated</td>
<td>No dose adjustments mentioned</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Contraindicated</td>
<td>No dose adjustments mentioned</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Limit to 5mg daily</td>
<td>No dose adjustments mentioned</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Initiate at 10mg daily</td>
<td>No dose adjustments mentioned</td>
</tr>
</tbody>
</table>
Combined Therapy with Atorvastatin and Calcineurin Inhibitors: No Interactions with Tacrolimus

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Introduction

Since life- and graft-threatening complications early after transplantation have been largely reduced, cardiovascular disease has become the main cause of death with a functioning graft (1,2). The incidence of dyslipidaemia, a well-known and frequent risk factor for atherosclerotic disease in the general population, is even higher in transplanted patients. Hence not surprisingly, therapy with statins is frequently started in these patients, given the well-established efficacy of statins in the prevention of cardiovascular disease in various patient cohorts, including renal transplant recipients (3–7).
Statin Therapy and CNIs

- Statins have been safely used in transplant recipients receiving cyclosporine when used at conservative doses
  - Close monitoring for myalgias/LFTs
  - LDL reduction to goal is not always achieved
  - Package insert for certain statins state that cyclosporine is a contraindicated combination

Safety and Efficacy of Atorvastatin in Heart Transplant Recipients

• Evaluated 150 patients on lipid lowering therapy
  – Safety and efficacy of higher dose atorvastatin in a group of statin-refractory patients
  – 48 patients were on atorvastatin
    • 69% of the patients initiated at 20mg dose
  – Myalgias, rhabomyolysis, myositis occurred in 4 patients
  – All adverse events occurred within the first 3 months of therapy

Safety and Efficacy of Atorvastatin in Heart Transplant Recipients

• Noted increased efficacy of 20mg dose for LDL lowering effects and appears to be safe with close monitoring

What does all of this mean?
What are my Safest Options for Statin Therapy?

• “In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with pravastatin, therapy should be initiated with 10 mg/day and titration to higher doses should be performed with caution”

• "Cyclosporine increased rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of Crestor should not exceed 5mg once daily”
Statins Therapy and CNIs

- Statins are beneficial in our transplant patients
- Can be used safely at low to moderate doses
- Caution when using high dose statins in Cyclosporine
  - All patients should be warned of possible ADEs and drug held/discontinued if any myalgias
Individual Drug Interactions
Pomegranate and FK/CyA

- Pomegranate has been used in other cultures for centuries for its many suspected health benefits

- Emerged more recently in US for anti-oxidant and anti-inflammatory properties
  - Thought to reduce cardiovascular disease, suppress prostate and breast cancers
Pomegranate and FK/CyA

- Very little literature exists
  - Most studies conducted in rats
  - A couple single case reports of interactions

- Farkas, et al. reported that one single bolus of pom juice did not alter 3A4
  - Participants were given 8oz of juice and either IV or PO midazolam at varying doses
  - Found that the consumption of pom juice did NOT alter activity of hepatic or intestinal CYP3A

Pomegranate and FK/CyA

• No solid evidence to prove that Pomegranate can affect FK or CyA levels

• Always use drug monitoring to ensure stable levels
What other non traditional medications might interact?
What about marijuana?

• As of December 2015, 4 states have legalized recreational marijuana use
  – Alaska
  – Washington
  – Oregon
  – Colorado

• Utilization is up as a whole
  – 2002: 4.1%
  – 2012: 9.5%

Marijuana and P-gp

• P-gp dependent ATPase activity assay is used in vitro to measure the affinity of compounds for P-gp
  – If alterations in the P-gp ATPase activity occurs, implies that a compound has affinity for P-gp
    • Potential substrate and/or inhibitor of P-gp

• Results revealed that all four cannabinoid compounds tested exhibited some degree of ATPase stimulation

Tacrolimus and Marijuana

67 yr old s/p HSCT
- Uneventful conditioning and transplant

FK level consistently supratherapeutic
- Day 10, admits to eating marijuana gummies

Despite dose decreases, level continues to rise
- FK level 45.8ng/mL on Day 23

Take Home Points You Already Know…

• Our patients are very complex!
  – Surgically/Medically
  – Medications
    • Polypharmacy
    • Multiple Interactions
    • Patient factors contribute daily
      – Non-compliance
      – GI side effects
Other Take Home Points

• Essentially any medication can be used, despite a drug interaction *if*:
  
  – You are ready and willing to monitor closely
    • Patients location/OSH can get in the way of safely monitoring
  
  – You know the time frame/other factors for when you will see an interaction/problem
Patient Case

- 30 year old female s/p BOLTx in April 2016
  - Tacrolimus 1mg every 12 hours
    - Levels have been stable between 10-12ng/mL
  - Mycophenolate mofetil 1000mg twice daily
  - Prednisone 10mg once daily
  - TMP/SMX DS 1 tablet daily Mon, Wed, and Fri
  - Voriconazole 200mg every 12 hours
  - Nifedipine XL 30mg once daily
  - Escitalopram 10mg daily at bedtime
Hospital Rounds

- 30 year old female s/p BOLTx in April 2016
  - The patient is admitted to the hospital with elevated LFTs, nausea/vomiting, and vision change
  - The team wants to stop the Voriconazole

WHAT DO YOU RECOMMEND?
Clinic Follow-up

• 30 year old female s/p BOLTx in April 2016
  – Patient has been put on Posaconazole
  – Returns to clinic 1 week after starting therapy

• Tacrolimus level is now 19.8ng/mL and the patient’s SCr and K+ are elevated

WHAT DO YOU RECOMMEND?
Clinic Follow-up

• 30 year old female s/p BOLTx in April 2016
  – The patient had completed the course of Posaconazole
  – The patient returns to clinic and is admitting to using marijuana
    • Her level is now 15.2ng/mL, K+ is 5.7

WHAT DO YOU RECOMMEND?
Transplant Medications: Review of Interactions

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