Drug Interactions in the Transplant Patient

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Nurse Practitioners Symposium
Nashville, TN
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Objectives

1.) Discuss the CYP 450 enzymes and common drug interactions with the immunosuppressants

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

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

4.) Review patient case
Patient Case

• 30 year old female s/p DLTx in April 2014
  – Tacrolimus 1mg twice daily
    • Levels have been stable between 10-12ng/mL
  – Mycophenolate mofetil 1000mg twice daily
  – Prednisone 5mg once daily
  – TMP/SMX DS 1 tablet daily Mon, Wed, and Fri
  – Itraconazole suspension 20mls twice daily
  – Lisinopril 5mg daily
  – Escitalopram 10mg daily at bedtime
Hospital Rounds

- 30 year old female s/p DLTx in April 2014
  - The patient is admitted to the hospital with elevated LFTs and nausea/vomiting
  - The team wants to stop the *Itraconazole suspension 200mg twice daily*

WHAT DO YOU RECOMMEND?
Clinic Follow-up

• 30 year old female s/p DLTx in April 2014
  – Patient has been put on Voriconazole
  – Returns to clinic 1 week after starting therapy

• Tacrolimus level is now 18.3ng/mL and the patient’s SCr and K+ are elevated

WHAT DO YOU RECOMMEND?
Clinic Follow-up

- 30 year old female s/p DLTx in April 2014
  - The patient had completed the course of voriconazole
  - The patient returns to clinic and is now hypertensive

- Initially, the MD wants to add **Diltiazem 180mg twice daily**

**WHAT DO YOU RECOMMEND?**
CAVEAT....

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

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

• Consistent 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
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

Unfortunately….

• The likelihood of a drug interaction increases with the number of medications a patient is taking

• Interactions are unavoidable for transplant patients
  – Routinely use medications that interact
  – Polypharmacy is an everyday part of a transplant patients regimen
  – 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….they seem to like manage them or maybe they just make things up.
Factors That Contribute to Drug Interactions

• **Time course of drug interactions**
  – Important for patient 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

Factors That Contribute to Drug Interactions

• Drug interactions occur during the absorption of drugs 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
Drug interactions: CYP Enzymes

Proportion of Drugs Metabolized by P450 Enzymes

- CYP2D6: 19%
- CYP1A2: 11%
- CYP2C19: 8%
- CYP2C8/9: 16%
- CYP2B6: 3%
- CYP2E1: 4%
- 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

<table>
<thead>
<tr>
<th>CYP450 3A4 Inducers</th>
<th><strong>Inducers DECREASE Tacrolimus/Cyclosporine Levels</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-convulsants</strong></td>
<td><strong>Anti-tuberculosis Agents</strong></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Rifampin</td>
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<tr>
<td>Phenobarbital</td>
<td>Rifabutin</td>
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<tr>
<td>Carbamazepine</td>
<td>Isoniazid</td>
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<tr>
<td><strong>Anti-biotics</strong></td>
<td><strong>Others</strong></td>
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<tr>
<td>Nafcillin</td>
<td>Ticlopidine</td>
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<td></td>
<td>St. Johns Wart</td>
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<td></td>
<td>Sirolimus (FK)</td>
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<td>Caspofungin (FK)</td>
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</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**

<table>
<thead>
<tr>
<th>Calcium Channel Blockers</th>
<th>Anti-arrhythmic Agent</th>
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<tbody>
<tr>
<td>Diltiazem</td>
<td>Amiodarone</td>
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<tr>
<td>Verapamil</td>
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<tr>
<td>Nicardipine</td>
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<tr>
<td>&quot;Azole” Antifungals</td>
<td>Immunosuppressive Agents</td>
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<tr>
<td>Fluconazole</td>
<td>Sirolimus (CyA)</td>
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<tr>
<td>Itraconazole</td>
<td></td>
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<tr>
<td>Ketoconazole</td>
<td>Protease Inhibitors</td>
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<tr>
<td>Posaconazole</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Indinavir</td>
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<tr>
<td>&quot;Mycin” Antibiotics</td>
<td>Nelfinavir</td>
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<tr>
<td>Erythromycin</td>
<td>Ritonavir</td>
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<tr>
<td>Clarithromycin</td>
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<tr>
<td>Food</td>
<td></td>
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<tr>
<td>Grapefruit</td>
<td></td>
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<tr>
<td>Blood Oranges</td>
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<tr>
<td>Pomegranate?</td>
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</tbody>
</table>
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
Individual Drug Interactions
AZOLE Anti-fungals

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

• Second generation triazole antifungal agent
  – Activity against *Candida, Aspergillus* spp, *Fusarium* spp

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

• Half-life
  – Variable and dose dependent

• Therapeutic Drug Monitoring should be considered

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
Posaconazole: Points to Consider

- Extended coverage including *Zygomycetes*
- Available as a suspension
- Food significantly increases the bioavailability
  - High fat meals had best systemic exposure
  - Should always be administered with meals

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 trough sirolimus levels without toxicity

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

# Recommended 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>
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<td></td>
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<tr>
<td>Posaconzole</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
Non-Dihydropyridine Calcium Channel Blockers

• Diltiazem
  – Tiazac, Cardizem CD, Cardizem LA, Dilacor XR

• Verapamil
  – Verelan, Calan SR, Covera
Diltiazem

• Often used as a first line agent, depending on organ group and indication
  – Dominant dilatory effect on afferent glomerular arteriole, where CNi vasoconstriction occurs

• High inter-patient variability

• ADEs of diltiazem often limit its use
  – Verapamil fallen out of favor due to ADEs

Diltiazem

- Diltiazem is a substrate for p-glycoprotein
- Has been shown to increase the tacrolimus concentrations by up to four-fold in animal models
  - Some case reports have reported a similar increase in humans
  - IV vs. Oral administration and dose make a difference

Diltiazem and Cyclosporine

- Determine if there was a relationship in diltiazem dose and blood concentration of CyA
  - Tested in renal transplant pts
  - Starting doses -- Diltiazem 30mg
  - Max dose tested was 180mg

- “Cyclosporine sparing effect was evident at doses of diltiazem lower than those currently used for the majority of transplant recipients”

Diltiazem and Cyclosporine

• “For transplant recipients receiving diltiazem in a dose >180mg per day, we recommend a cautious approach to dosage reduction”
  – Potential harm resulting from cyclosporine blood concentrations falling below the therapeutic range is significant

What does all of this mean?
Diltiazem...Things to Consider

• Consider diltiazem starting dose – Lower doses may not require a CNI dose reduction
  – Increasing the dose may increase immunosuppression levels over time
  – High inter-patient variability

• Brockmoller, *et al* suggest a 45% increased CyA concentration
  – Noted in 19 of 22 renal tx pts

• Drug monitoring is key

Individual Drug Interactions
Proton Pump Inhibitors (PPIs)
PPIs and Mycophenolate mofetil

• Current controversial topic
  – Conflicting findings within literature
  – Also conflicting data between different PPIs

• Gastroesophageal reflux disease is common s/p lung transplant
  – Estimated incidence nearly 75%¹

• Estimated that ~40% of heart recipients suffered from GI complaints
  – 86% of those pts were treated with a PPI²

Proton Pump Inhibitors Reduce MMF Exposure in Heart Transplant Recipients – A Prospective Case – Controlled Study

- Kofler, et al followed 22 heart tx recipients
  - All pts received MMF 1000mg twice daily and pantoprazole 40mg daily
  - Measured MPA-plasma concentrations measured vial blood draws: redose, 30mins, 1 hour, and 2 hours
  - Measured again 1 month after stopping PPI

Kofler, et al -- Results

- MMF blood concentration time profiles of MPA with and without pantoprazole 40mg

Kofler, et al. Continued

- **Conclusions**
  - “The present study shows that the usual therapeutic dose of pantoprazole 40mg had a significant influence on the maximal MPA plasma concentration”
  - “The total MPA-AUC could be increased by 34% after PPI withdrawal”
Proton Pump Inhibitor Co-medication Reduces Active Drug Exposure in Heart Transplant Recipients Receiving Mycophenolate Mofetil

- Followed 19 transplant patients
  - Mean time s/p OHTx was 2.3 yrs
  - Adjusted MMF dose to target trough levels of 1-4mg/L
  - All patients received pantoprazole
  - MMF levels measured when pts were on PPI and then 1 month after stopping

- Results
  - Found significantly lower MMF troughs/AUCs during PPI therapy vs. PPI-free

Dose-adjusted MPA AUCs with or without PPI co-medication

N= 19

Omeprazole Impairs Absorption of Mycophenolate Mofetil But Not of Enteric-Coated Mycophenolate Sodium in Healthy Volunteers

- Measured drug bioavailability in 12 healthy study volunteers (6 male/6 female)
  - **Study A:** MMF 1000mg with and without omeprazole 20mg twice daily
  - **Study B:** EC-MPS 720mg with and without omeprazole 20mg twice daily
  - Chose highest recommended dose of omeprazole to maximize interaction

Results

Omeprazole Impairs Absorption of Mycophenolate Mofetil But Not of Enteric-Coated Mycophenolate Sodium in Healthy Volunteers

**Conclusion**

- “Incomplete dissolution of mycophenolate mofetil at elevated gastric pH is responsible for the decreased absorption of MPA with co-administered PPIs in volunteers”

- “The absorption of EC-MPS is not affected”

The Role of Proton Pump Inhibitors on Early Mycophenolic Acid Exposure in Kidney Transplantation: Evidence from the CLEAR Study

- **CLEAR Study – 126 Adult kidney transplant recipients**
  - Six month, open-label, prospective, randomized, controlled, multicenter study conducted in 9 centers in Canada
  - **Treatment arm (N=65):** Loading dose of MMF 1500mg twice daily until POD 5, then 1000mg twice daily
    - 61.5% received a PPI
  - **Control arm (N=61):** MMF1000mg twice daily
    - 54.1% received a PPI

The Role of Proton Pump Inhibitors on Early Mycophenolic Acid Exposure in Kidney Transplantation: Evidence from the CLEAR Study

- Study was not powered to assess MPA exposure and absorption in patients receiving versus not receiving PPI therapy
  - Patients not randomized to PPI therapy/dosing

- Conclusion
  - PPI therapy in combination with MMF does not appear to have a significant impact on early MPA exposure

Kiberd BA, et al. *Ther Drug Monit.* 2011;33:120-123
What does all of this mean?
Mycophenolate and PPIs: Things to Consider

- Recent studies have demonstrated decreased MPA exposure with co-administration of PPI
  - Healthy volunteers, heart, and kidney recipients

- All authors recommend therapeutic drug monitoring if there is concern for adequate levels

- Drug monitoring is difficult
  - Full MPA-AUC requires multiple blood draws
  - Not feasible in clinical practice
Individual Drug Interactions
Statins and FK/CyA

- 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

Statins and FK/CyA

• 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

Statins and FK/CyA

- Statins have been safely used in transplant recipients receiving cyclosporine when used at conservative doses
  - Close monitoring for myalgias
  - LDL reduction to goal is not always achieved
  - Package insert for simvastatin states 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?
Statins and FK/CyA

- 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
I’m not convinced we’ve wasted enough time on this.
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
  – 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

What does all of this mean?
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
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
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