Prescribing to Patients with Renal Diseases

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How to Compute Risk

Risk = product of probability of the hazard

- (likelihood of event occurring) x (impact of event occurring)

- both items are considerably higher in kidney disease patients
Characteristics of kidney disease patients

- Kidney disease not being recognised
- Multiple comorbidities
- Polypharmacy and complicated regime
- Change in volume of distribution $V_d$ of many hydrophilic drugs
- Receiving medication with inadequate (or conflicting) drug dosing guide
- May experience accumulation of metabolites (besides parent compound)

How many are they taking

17 drugs at 8 am
Another Example

17 drugs at 8 am

Medication errors in chronic kidney disease: one piece in the patient safety puzzle

Jeffrey C. Fink and Glenn M. Chertow

See original article on page 1192
Case 1: Confused Lady

A 63-year-old female presented with three-day history of confusion together with visual and auditory hallucination

Diabetes mellitus and end-stage renal disease on continuous ambulatory peritoneal dialysis CAPD

Confused Lady

Recently she had developed vesicular rash over T4 dermatome and was treated with oral acyclovir 800 mg 5 times daily
She had neither fever nor meningism
Computed tomography of the brain showed old infarct only
Acyclovir neurotoxicity

Acyclovir neurotoxicity *versus* zoster-associated encephalitis (typically delirium within days following the vesicular eruption)

Failure to recognize the diagnosis of acyclovir neurotoxicity may lead to coma with continued systemic acyclovir therapy

How to diagnose

Acyclovir neurotoxicity should always be considered in those patients with concomitant chronic kidney disease but without dose adjustment
Pharmacology

Acyclovir excretion is predominantly renal (by glomerular filtration and tubular secretion)
Low volume distribution and low protein binding
As a result, the plasma half-life of acyclovir can increase from 2.9 to 19.5 hours in patient with end-stage renal disease


How they present

Lethargy 30%
Confusion 30-42%
Agitation 26%
Hallucination 26%
Myoclonus 30%
Dysarthria 16%
Seizures 3.3%

Acyclovir metabolite

Serum levels of acyclovir are unhelpful for monitoring risk of neurotoxicity
Often comes with a delay of 24-48 hours after the peak acyclovir dose
Acyclovir metabolite 9-carboxymethoxymethylguanine (CMMG) more predictive of neuropsychiatric side effects

Effects of metabolite

Drug metabolites may result in unforeseen consequences (quite significant pharmacologic activities for certain metabolites)
Pharmacokinetics and pharmacodynamics of metabolites not often fully evaluated during clinical trials
CKD patients are receiving...

A new pharmacologic entity

Parent compound + Metabolites

Markedly different from those reported in patients with normal renal function

Example of morphine toxicity

- Yes, morphine itself is predominantly metabolized by liver
- Mind you, metabolites (morphine-3-glucuronide and morphine-6-glucuronide) accumulate in patients with renal impairment and they are at least as potent as their precursors (delirium, drowsiness, respiratory depression)
What can be Done

- Better recognition of drug dose adjustment from post marketing surveillance, and most importantly, education
- If not sure, check for reference (such as British National Formulary, electronic gadgets)
- Support system (computerized)

Beta-lactam antibiotics

Newer medication

Cefepime neurotoxicity is diagnosed with much more delay than ceftazidime neurotoxicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cefepime-treated</th>
<th>Ceftazidime-treated</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (years)</td>
<td>60.4 ± 10</td>
<td>58.1 ± 12</td>
<td>0.54</td>
</tr>
<tr>
<td>M/F</td>
<td>13/2</td>
<td>12/3</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mean ± SD (mg/dL)</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Concurrent conditions, no. (%)</td>
<td>9 (21)</td>
<td>5 (42)</td>
<td>0.25</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>5 (12)</td>
<td>4 (39)</td>
<td>0.05</td>
</tr>
<tr>
<td>Transplant renal failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Clinical features, no. (%)</td>
<td>8 (14)</td>
<td>5 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Confusional</td>
<td>20 (53)</td>
<td>11 (19)</td>
<td>1.00</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>12 (29)</td>
<td>5 (8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Electrophysiological findings, no. (%)</td>
<td>21 (50)</td>
<td>3 (6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus</td>
<td>13 (30)</td>
<td>6 (12)</td>
<td>0.17</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>6 (14)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Length of stay before symptoms onset</td>
<td>5 (4-10)</td>
<td>6.5 (4-11)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time between symptoms onset and diagnosis</td>
<td>5 (4-9)</td>
<td>3 (2-6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration of symptoms, median (IQ range)</td>
<td>8 (5-10)</td>
<td>4 (4-6)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Cefepime

- concentration of cefepime in spinal fluid rises in patients with renal failure
- due to competitive inhibition of the active transport of cefepime from the cerebrospinal fluid to the blood by:
  1. accumulation of toxic organic acids
  2. increased blood-brain barrier permeability
  3. low serum protein binding


What FDA says ... finally

- FDA received 59 reports of nonconvulsive status epilepticus in cefepime users with renal impairment (most of whom did not have dosage adjusted)
- Clinicians should adjust the dose of cefepime in patients with creatinine clearance ≤ 60 ml/minute

FDA Drug Safety Communication, posted 06/26/2012
**Mechanism**

- main mechanism of cephalosporin neurotoxicity involves a decrease in the release of GABA (main inhibitory neurotransmitter in central nervous system)
- inhibition of GABA receptors by beta-lactams leads to hyperexcitability of neurons and reduces the seizure threshold

**How about penicillin**

- Penicillins: bind reversibly to GABA
- Cephalosporins: bind irreversibly (which explains their greater potential to cause neurotoxicity)
Support System

Patient-specific creatinine clearance data transferred to the computer system, enabling it to trigger an alert when a potential medication error is detected.
Target drugs for alert

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Drug Intervention</th>
<th>Potential Risks if Drug Intervention Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>&lt; 25</td>
<td>Adjust dosage</td>
<td>Seizures, somnolence, confusion</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Hypersensitivity syndrome, xanthine stone formation</td>
</tr>
<tr>
<td>Aminumidine</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Nausea, vomiting, slurred speech, hallucinations</td>
</tr>
<tr>
<td>Ciprofloxacain</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Acute renal failure, seizures</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Seizures, somnolence, confusion</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Drowsiness, lethargy, double vision, slurred speech</td>
</tr>
<tr>
<td>Glyburide</td>
<td>&lt; 51</td>
<td>Avoid use</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Acute renal failure, seizures</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>&lt; 40</td>
<td>Adjust dosage</td>
<td>Drowsiness, extrapyramidal symptoms, seizures</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>&lt; 40</td>
<td>Avoid use</td>
<td>Peripheral neuropathy, vomiting, ineffective therapy</td>
</tr>
<tr>
<td>Pencicarbidone</td>
<td>&lt; 51</td>
<td>Adjust dosage</td>
<td>Bradycardia, QT prolongation, torsade de pointes</td>
</tr>
<tr>
<td>Sotalolatin</td>
<td>&lt; 10</td>
<td>Avoid use</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>&lt; 30</td>
<td>Adjust dosage</td>
<td>Nausea, vomiting, confusion</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>15 to &lt; 30</td>
<td>Adjust dosage</td>
<td>Nausea, vomiting, hematuria, crassula</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>&lt; 15</td>
<td>Avoid use</td>
<td>Nausea, vomiting, hematuria, crassula</td>
</tr>
</tbody>
</table>

Table 1. The Drug Renal Alert Program's Target Drugs and Their Respective Creatinine Clearance Threshold Values, Recommended Drug Interventions, and Potential Risks.7-10

To the List, We Add

- Tranexamic acid
- Clarithromycin
- Cefepime
- Tramadol
- Baclofen
- Low molecular weight heparin
Support System

- Real-time decision computerized decision support system (for prescribing in patients with renal diseases)
- Study of 97,151 orders on medication cleared by kidney (or nephrotoxic ones)
- Appropriate prescriptions 67% versus 54% ($p < 0.01$)
- Mean length of stay 4.3 versus 4.5 days ($p = 0.009$)

Stepwise Approach

Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)


Table 3: Stepwise approach to adjust drug dosage regimens for patients with CKD and ARF

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Obtain history and relevant demographics/clinical information</td>
</tr>
<tr>
<td>Step 2</td>
<td>Estimate GFR</td>
</tr>
<tr>
<td>Step 3</td>
<td>Review current medications</td>
</tr>
<tr>
<td>Step 4</td>
<td>Calculate individualized treatment regimen</td>
</tr>
<tr>
<td>Step 5</td>
<td>Monitor</td>
</tr>
<tr>
<td>Step 6</td>
<td>Revise regimen</td>
</tr>
</tbody>
</table>

Abbreviations: ARF, acute renal failure; CKD, chronic kidney disease; CL\textsubscript{cr}, creatinine clearance; eGFR, estimated GFR; GFR, glomerular filtration rate.

Evidence base medicine

Extra consideration in kidney disease patients
Statins for dialysis patients

- Bad news for the pharmaceutical companies

- Two moderately large trials of statins in dialysis populations (both in *N Engl J Med*) did not show reduction in total mortality despite substantial lowering of serum LDL cholesterol

4D Study

- 1255 hemodialysis patients with type 2 diabetes and elevated serum LDL cholesterol levels randomly assigned to placebo or atorvastatin 20 mg/day

- Successfully lowered LDL cholesterol (3.1 to 1.9 mmol/L)

- Median follow-up of 4 years: no difference in the incidence of the primary outcome (cardiovascular death, nonfatal myocardial infarction, and stroke)

AURORA Trial

- 2776 hemodialysis patients not being treated with a statin randomly assigned to rosuvastatin 10 mg/day or placebo
- successfully lowered mean serum LDL levels at 3 months (2.6 to 1.5 mmol/L)
- median follow-up 3.8 years: similar incidence of primary composite end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)
- no benefit for any prespecified subgroup, including diabetes or elevated C-reactive protein levels


Explanations

- Different pathogenic processes for adverse cardiovascular outcomes among patients with end-stage renal disease (from those with either mild to moderate renal dysfunction or normal kidney function)
- In the dialysis population, ~60% of all cardiac deaths presumably due to heart failure, sudden death or arrhythmias (and statin might not work in such cases), rather than atherosclerotic CVD events
Dilemma

- Pitfall of extrapolating data from populations with normal kidney function
- Another good example would be diabetes care/glycaemic control in patients with chronic kidney disease

Diabetes control in CKD patients - another example
Glucose Control

- Only recommend a target HbA1c ~ 7% to prevent or delay progression of microvascular complications, including diabetic kidney disease

- Special consideration in advanced CKD - recommend not treating to HbA1c target < 7% in patients at risk of hypoglycaemia

Why increase hypoglycemia

Stage 4 or 5 CKD

- Decreased clearance of insulin (and oral agents) [one-third of insulin degradation is carried out by kidneys]

- Impaired renal gluconeogenesis with reduced kidney mass
Oral sulphonylurea

First generation sulphonylurea

- Chlorpropramide, tolbutamide
- Rely on kidneys to eliminate both parent drug and active metabolites
- To be avoided altogether in patients with chronic kidney disease

Second generation sulphonylurea

- Glipizide, gliclazide, glimepiride
- Choose the one that does not have its active metabolites (such as glipizide and gliclazide)
Metformin

- Most authorities have recommended a GFR cut-off of < 60 ml/min/1.73 m²

- Too restricted use of metformin?
Metformin - cleared by kidney

- Clearance of metformin decreases by ~75% when GFR < 60 ml/min/1.73 m²
- No further change when GFR declines to 30 ml/min/1.73 m²
- At GFR 30-60 ml/min/1.73 m²: serum concentration of metformin only two-fold higher than in normal kidney function


Meta-analysis

- Pooled data from 347 trials and cohort studies
- No cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use
- Poisson statistics: upper limit of true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases (metformin group) and 5.4 cases (non-metformin group)

Observational study

- No randomised trial of metformin among chronic kidney disease patients
- Mostly depend on observational data
- Important insight from a large European database
- Hospital outpatient clinic and primary care in Sweden, 2004-2010, mean follow-up 3.9 years
- 51,675 patients with type 2 diabetes


Metformin

- Metformin associated with
  - reduced risk of CVD, acidosis/serious infection and all-cause mortality compared with insulin
  - reduced risk of all-cause mortality compared with other oral hypoglycaemic agents

Large cohort study

- Effects consistent in patients with renal impairment (eGFR 45-60 ml/min/1.73 m²)

- And no increased risk of acidosis/serious infection even in patients with low renal function (eGFR 30-60 ml/min/1.73 m²)

New recommendation

- Metformin use re-evaluated when GFR < 45 ml/min/1.73 m²
- Stopped when GFR < 30 ml/min/1.73 m²
- Adopted by British National Formulary

Case 2: Another Slow Man

A 81-year-old ESRD patient was transferred back from convalescent hospital for review of his CAPD technique (borderline)

Investigation showed hypercalcaemia

Adjusted calcium 2.77 mmol/L
A Glance at Drug Chart

Calcium carbonate one tablet daily
Alfacalcidol 1 microgram daily
Furosemide 250 mg daily
Ferrous sulphate 300 mg daily
Prazosin 0.5 mg nocte

Alfacalcidol

Vitamin D analogs (1α-hydroxyvitamin D₃) used to treat secondary hyperparathyroidism

Most evidence from oral pulse vitamin D therapy (not daily maintenance)

Alfacalcidol

Alfacalcidol 1 microgram daily!

Original prescription as read from computer record:
Alfacalcidol 1 microgram(s) om (1 days per week)

What Happened

Patient admitted to medical (non-renal) ward on 26.4.2011
The admission house officer transcribed the medication to drug sheet by copying 1 microgram daily (without noticing the supplementary wording of “1 day per week”)
Continued at transferal to Shatin Hospital on 2.5.2011
Discrepancy noted only when the patient returned to renal ward on 7.5.2011
Learning Points

Unusual drug frequency
Uncommon medication – at least for a medical intern
Patient had cognitive impairment to voice out the 7-times higher dispensing of alfacalcidol

That reminds us of Methotrexate

Dozens of fatalities reported in patients who misunderstands/were prescribed by mistake methotrexate daily instead of weekly
Steps to Take (Weekly Drugs)

- Obtain correct medication history
- Automated alerts (electronic prescribing systems)
- Explicit dosing instruction
- Patient counseling (new or modified prescription before discharge) - verbal and not just written information
- Educate practitioners

Methotrexate and renal failure

**Case Report**

Fatal Pancytopenia in a Hemodialysis Patient After Treatment With Low-Dose Methotrexate

Kitty Kit Ting Cheung, MBChB,† Kai Ming Chow, MRCP, Cheuk Chan Szeto, FRCP, MD,†
Morris Hok Leung Tai, FRCP,A,† Bonnie Ching Ha Kwan, MRCP,†
and Philip Kam Tso Li, FRCP, FACP, MD*  

Never prescribe methotrexate in patients with creatinine clearance < 10 ml/min please!  
Not even weekly
Methotrexate and renal failure

TABLE 1. Clinical Details of Renal Failure Patients With Methotrexate-Induced Nephrotoxicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Erythrocyte</th>
<th>Clinical</th>
<th>Features</th>
<th>Management</th>
<th>Methotrexate</th>
<th>Features</th>
<th>Management</th>
<th>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>F</td>
<td>RA</td>
<td>Fever, cough, myalgia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>RA</td>
<td>Fever, cough, myalgia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Methotrexate and renal failure

TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Erythrocyte</th>
<th>Clinical</th>
<th>Features</th>
<th>Management</th>
<th>Methotrexate</th>
<th>Features</th>
<th>Management</th>
<th>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>8</td>
<td>M</td>
<td>RA</td>
<td>Fever, cough, myalgia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>M</td>
<td>RA</td>
<td>Fever, cough, myalgia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA = not available, RBC = red blood cell, AST/ALT = aspartate aminotransferase, ALT, WBC = white blood cell, TUL = total urea level, TAL = total albumin level.*
What about Patients on Dialysis

- Haemodialysis
- Peritoneal dialysis

CRRT (continuous renal replacement therapy) beyond the scope of discussion today

Haemodialysis

- Not much reliable information from well-designed pharmacokinetic studies on optimal drug dosing in patients receiving intermittent haemodialysis (an artificial “kidney” that can eliminate drugs)
Drug characteristics

- Molecular weight or size (more dialyzable for small molecules)
- If we use low-flux membranes, drugs > 1,500 Daltons will have limited diffusive clearance in haemodialysis

P.S. Most drugs have a molecular weight < 500 Daltons

Drug characteristics

- Degree of protein binding (less dialyzable for highly protein bound drugs, say > 60%)

Remember that molecular weight of albumin is 68,000 Daltons (and therefore only unbound fraction of a drug is cleared)
Haemodialysis

Drug characteristics

- Distribution volume
  (A large $V_d$ means that a drug distributes outside of plasma, and therefore only a small proportion could be cleared)
- Drug solubility (lipid-soluble drugs have reduced clearance)

Dialysis factors

- Blood and dialysate flow rates
- Composition of dialysis filter
  (predominantly semisynthetic and synthetic materials nowadays)
- Filter surface area
  (High flux dialysis membrane have larger pores and allows passage of most solutes, including those $\leq 20,000$ Daltons)
Haemodialysis

To further complicate the issue

- Some drugs adhere to dialysis membrane
- Non-renal clearance (metabolism) of some drugs altered by haemodialysis

Example of erythromycin

A single 4-hour session of haemodialysis shown to increase non-renal clearance of erythromycin in ESRD patients by 27% as soon as 2 hours after HD

Example of erythromycin

Mechanism proposed

- Removal of uraemic solutes (that accumulate during interdialytic period and inhibited CYP450 3A4 and drug transporters)


Steps We can Take

- Better PK/PD study to determine haemodialysis clearance for drugs that will likely be used in ESRD patients
- Extrapolate from existing studies (studies conducted before 2000 probably underestimate)
Steps We can Take

- Give the drug after dialysis (to ensure active drug levels until next dosing), consider supplementary dose
- Therapeutic drug monitoring for drugs with narrow therapeutic range (aminoglycoside, vancomycin)

Example of sodium valproate

- A 23-year-old female haemodialysis patient
- Epilepsy since age of 5 years
- Partial complex seizures after dialysis sessions (after change to a method call haemodiafiltration HDF)

Peritoneal Dialysis

- Most typical peritoneal dialysis prescriptions designed to achieve a urea clearance of around 10 ml/min
- Most drugs are larger than urea (and their clearance is even less)

Drug clearance will likely be in the range of 5 to 7.5 ml/min

Peritoneal Dialysis

For convenience (and simplicity)

follow the recommendation for those with creatinine clearance or eGFR < 15 ml/minute
Case 3: Orthopaedic Case

A 39-year-old man with ESRD
Previous right nephrectomy for Wilm’s tumor, non-recovery of renal function after Stevens-Johnson syndrome
Cadaveric renal transplant in 2006
Follow up Tuen Mun Hospital

Orthopaedic consultation

Right buttock mass, rapidly progression since August
MRI: large sarcoma arising from gluteus medius and minimus muscle
Referral to orthopaedic tumor team in our hospital
Immunosuppression changed to sirolimus
Sirolimus

- Mammalian target of rapamycin (mTOR) inhibitors
- Block the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation (c.f. tacrolimus and cyclosporine: inhibit the production of cytokines)

Sirolimus

- also inhibit proliferation of smooth muscle cells
- have anti-malignancy potential
Sirolimus and wound healing

Associated with wound dehiscence and impaired healing; use caution in the peri-operative period (especially with BMI >30 kg/m²)

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Tacrolimus group</th>
<th>Sirolimus group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative fluid collection</td>
<td>2</td>
<td>9</td>
<td>0.038</td>
</tr>
<tr>
<td>Superficial wound infection</td>
<td>1</td>
<td>11</td>
<td>0.004</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>0</td>
<td>8</td>
<td>0.005</td>
</tr>
<tr>
<td>Superficial wound dehiscence</td>
<td>0</td>
<td>4</td>
<td>0.051</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2</td>
<td>4</td>
<td>0.462</td>
</tr>
<tr>
<td>Seroma</td>
<td>0</td>
<td>1</td>
<td>0.335</td>
</tr>
<tr>
<td>Fascial dehiscence</td>
<td>1</td>
<td>4</td>
<td>0.201</td>
</tr>
<tr>
<td>Deep wound infection</td>
<td>0</td>
<td>2</td>
<td>0.171</td>
</tr>
<tr>
<td>Urinary leak</td>
<td>0</td>
<td>2</td>
<td>0.171</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Comparing the tacrolimus group with the sirolimus group.

Orthopaedic admission

Called back for operation of right pelvic chondrosarcoma
(when the patient remained on sirolimus immunosuppression)
**Progress**

Changed to cyclosporine before proceeding to wide local resection surgery (when nephrologist was consulted pre-operatively)

Others include hydrocortisone cover (and then prednisolone postoperatively)

Trough cyclosporine level 70 µg/L (suggested therapeutic range 70-100 µg/L)

**Complication**

Developed high temperature day 11 postoperatively

Associated chills, rigors

Blood pressure 100/60 mmHg

“Withhold anti-HT tonight”

Urgent medical consultation
Whole bunch of medication

Six pages of Medication Administration Record
Tramadol, pregabalin, cyclosporine, prednisolone, lactulose, Bisolvon, colchicine, clindamycin, metoprolol, prazosin, diltiazem

Medical review

Found out that patient was not on prednisolone for 6 days
(because of missed renewal when transcribing the medications by intern)
Six pages of drug charts
Implicit message of “Turf”

Hospital geography: “narrowly defined but visible boundary of turf”

“I’m going to see the patient as consultation basis; he isn’t MY patient.”

Diltiazem and cyclosporine

I didn’t realise that the patient had stopped taking diltiazem

Diltiazem is a potent CYP3A enzyme inhibitor (whereas cyclosporine is a substrate for CYP3A)

We expect a dramatic decrease in the cyclosporine level after discontinuing the diltiazem

### Table 2. Common Drug Substrates, Inhibitors, and Inducers of CYPIA, According to Drug Class.

<table>
<thead>
<tr>
<th>CYPIA Substrates</th>
<th>CYPIA Inhibitors</th>
<th>CYPIA Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers</td>
<td>Calcium-channel blockers</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Verapamil</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Azole antifungal agents</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Ketoconazole</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Fluconazole</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Immunosuppressant agents</td>
<td>Fluconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Fluconazole</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Fluconazole</td>
<td>Phenytion</td>
</tr>
<tr>
<td>Sertraline, SSRI</td>
<td>Fluconazole</td>
<td>Anti-HIV agents</td>
</tr>
<tr>
<td>Sertraline, SNRI</td>
<td>Fluconazole</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Ketoconazole</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Ketoconazole</td>
<td>Others</td>
</tr>
<tr>
<td>Statins</td>
<td>Ketoconazole</td>
<td>St. John’s wort</td>
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<tr>
<td>Atorvastatin</td>
<td>Ketoconazole</td>
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<td>Others</td>
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<tr>
<td>Others</td>
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<td>Macrolide antibiotics</td>
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<td>Others</td>
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<tr>
<td>Erythromycin</td>
<td>Ketoconazole</td>
<td>Others</td>
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<tr>
<td>Anti-HIV agents</td>
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</tr>
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<td>Others</td>
<td>Others</td>
</tr>
</tbody>
</table>

* These inhibitors and inducers can interact with any CYPIA substrate and may have important clinical consequences. HIV denotes human immunodeficiency virus.

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Risk of graft rejection

Sub-therapeutic cyclosporine level

Not to mention... the inadvertent discontinuation of prednisolone...
Take Home Message

Beware of dosage adjustment in patients with kidney disease

Changes in drug metabolism and clearance of certain drugs (and sometimes their toxic metabolites) can predispose patients with CKD to acute confusion states or neuropsychiatric symptoms

Clinical Pearls
Clinical Pearls

Extra caution in patients with polypharmacy (again, typical example being patients with kidney disease)

Knowledge gap in (unpredictable) drug dosing in patients on dialysis