Prescribing to Patients with Renal Diseases

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How to Compute Risk

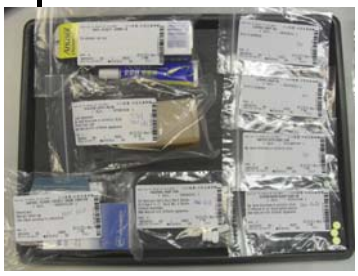
Risk = product of probability of the hazard

- (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

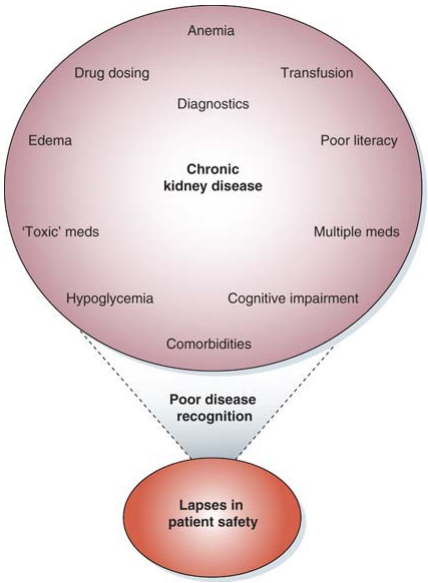
17 drugs at 8 am

http://www.kidney-international.org

see original article on page 1192

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

Jeffrey C. Fink[1] and Glenn M. Chertow[2]



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

Laskin OL. Clinical pharmacokinetics of acyclovir. Clin Pharmacokinet 1983;8:187-201.

How they present

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

Adair JC, Gold M, Bond RE. Acyclovir neurotoxicity: clinical experience and review of the literature. South Med J 1994;87:1227-1231.

Acyclovir metabolite

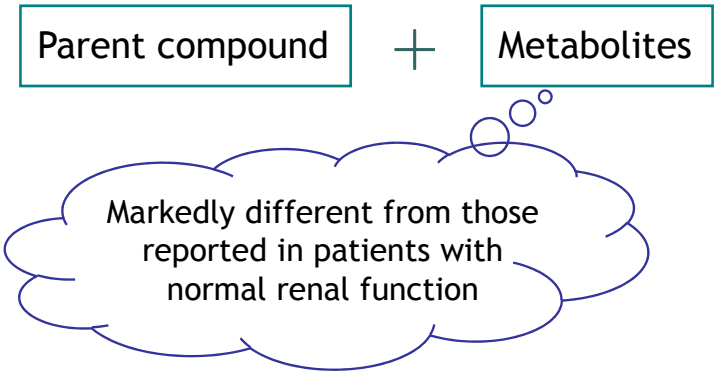
- Serum levels of acyclovir are unhelpful for monitoring risk of neurotoxicity
- Often comes with a delay of 24-48 hours after the peak acyclovir dose
- Acyclovir metabolite 9-carboxymethoxymethylguanine (CMMG) more predictive of neuropsychiatric side effects

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



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 gagdets)
- Support system (computerized)

Beta-lactam antibiotics

Table 1 Likelihood of neurotoxicity caused by beta-lactam antibiotics

Risk of neurotoxocity due to beta-lactam antibiotics[a]	Structural characteristics (see Fig. 2 for details)
High-risk agents	
Benzylpenicillin	
Cefazolin	Tetrazole derivatives and marked similarity with pentylenetetrazole
Cefoperazone	
Cefoselis	
Ceftazidime	Heterocyclic ring at position 3 and position 7 of 7-aminocephalosporanic acid
Cefepime[b]	
Medium-risk agent	
Ceftriaxone	Heterocyclic ring at position 3 and position 7
Low-risk agents	
Cefotaxime	One heterocyclic ring at position 7
Cefuroxime	
Cephalexin	Substitution of a heterocyclic ring at position 3 (R2) with small groups
Cephradine	

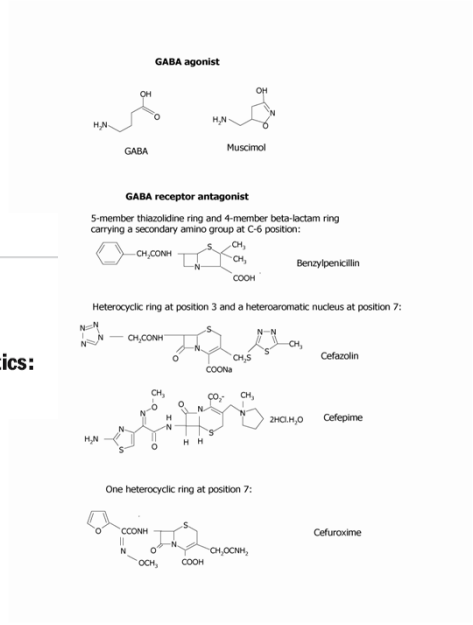
Chow KM, Hui AC,Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. Eur J Clin Microbiol Infect Dis 2005;24:649-653.

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-005-0021-y

REVIEW ARTICLE

K. M. Chow · A. C. Hui · C. C. Szeto

Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside



Newer medication

Cefepime neurotoxicity is diagnosed with much more delay than ceftazidime neurotoxicity

Table 2. Characteristics of 54 Patients with Neurotoxicity Induced by Cefepime or Ceftazidime

Characteristic	Cefepime-Treated Patients (n=42)	Ceftazidime-Treated Patients (n=12)	p Value
Age, mean ± SD (yrs)	61 ± 19	65 ± 13	0.57
M/F	17/22	7/5	0.51
Serum creatinine, mean ± SD (mg/dl)	8.3 ± 5.1	6.5 ± 3.7	0.33
Concurrent condition, no. (%)			
Received regular dialysis therapy	9 (21)	5 (42)	0.26
Acute renal failure	5 (12)	4 (33)	0.69
Transplant recipient (kidney, lung)	4 (10)	0	0.56
Clinical features, no. (%)			
Seizures	6 (14)	1 (8)	1.00
Confusion	39 (93)	11 (91)	1.00
Myoclonus	12 (29)	6 (50)	0.18
Electrophysiologic findings, no. (%)			
Encephalopathy	21 (50)	2 (25)	—
Nonconvulsive status epilepticus	15 (35)	6 (75)	0.17
Generalized seizures	6 (14)	0	—
Length of drug therapy before symptom onset, median (interquartile range) days	5 (4–10)	6.5 (4–11)	0.36
Time lag between symptom onset and diagnosis, median (interquartile range) days	5 (4–6)	3 (2–4)	0.005
Duration of symptoms, median (interquartile range) days	8 (5–10)	4 (4–6)	0.014

Chow KM, Szeto CC, Hui AC, Wong TY, Li PK. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. Pharmacotherapy 2003;23:369-373.

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

Chow KM, Szeto CC, Hui AC, Li PK . Mechanisms of antibiotic neurotoxicity in renal failure. Int J Antimicrob Agent, 2003;23:213-217.

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

Ciprofloxacin

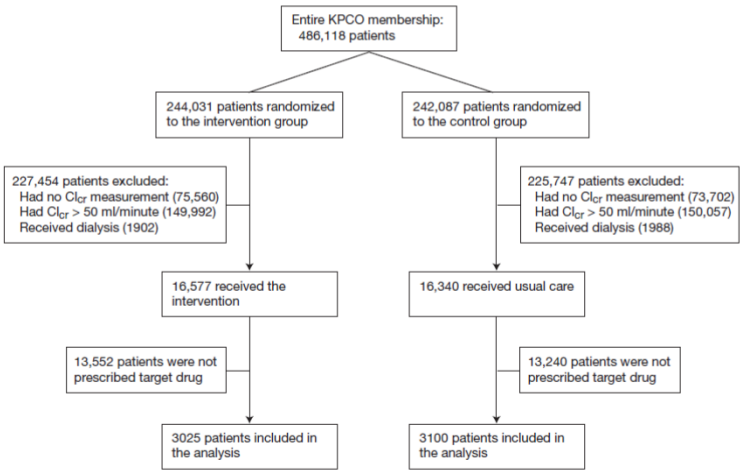
Interaction:
Dosage adjustment recommended for CIPROFLOXACIN when CrCl < 51 ml/min

CrCl (ml/min)	Recommended Dose
< 51	250-500 mg every 12 hours
<30	250-500 mg every 18-24 hours

CIPROFLOXACIN EXTENDED RELEASE TABLETS

Indication	CrCl (ml/min)	Recommended Dose
Complicated Urinary Tract Infection/Acute Uncomplicated Pyelonephritis	<30	500 mg every24 hours

Support System



Target drugs for alert

Table 1. The Drug Renal Alert Pharmacy Program's Target Drugs and Their Respective Creatinine Clearance Threshold Values, Recommended Drug Interventions, and Potential Risks[27–30]

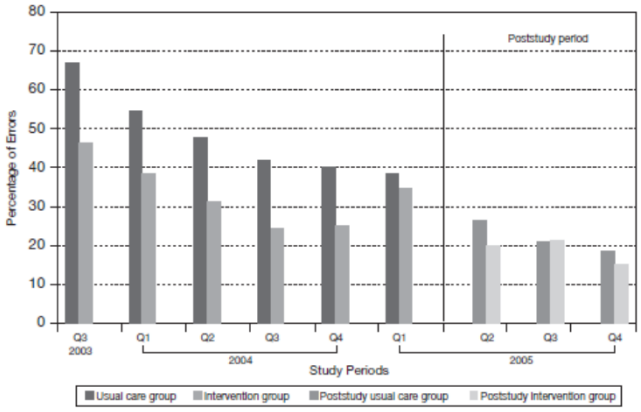
Drug	Creatinine Clearance (ml/min)	Drug Intervention	Potential Risks if Drug Intervention Not Done
Acyclovir	< 25	Adjust dosage	Seizures, somnolence, confusion
Allopurinol	< 51	Adjust dosage	Hypersensitivity syndrome, xanthine stone formation
Amantadine	< 51	Adjust dosage	Nausea, vomiting, slurred speech, hallucinations
Ciprofloxacin	< 51	Adjust dosage	Acute renal failure, seizures
Famciclovir	< 51	Adjust dosage	Seizures, somnolence, confusion
Gabapentin	< 51	Adjust dosage	Drowsiness, lethargy, double vision, slurred speech
Glyburide	< 51	Avoid use	Hypoglycemia
Levofloxacin	< 51	Adjust dosage	Acute renal failure, seizures
Metoclopramide	< 40	Adjust dosage	Drowsiness, extrapyramidal symptoms, seizures
Nitrofurantoin	< 40	Avoid use	Peripheral neuropathy, vomiting, ineffective therapy
Procainamide	< 51	Adjust dosage	Bradycardia, QT prolongation, torsade de pointes
Spironolactone	< 10	Avoid use	Hyperkalemia
Sulfasalazine	< 30	Adjust dosage	Drowsiness, dizziness, anorexia, nausea, vomiting
Trimethoprim	< 30	Adjust dosage	Nausea, vomiting, confusion
TMP-SMX	15 to < 30	Adjust dosage	Nausea, vomiting, hematuria, crystalluria
TMP-SMX	< 15	Avoid use	Nausea, vomiting, hematuria, crystalluria

TMP-SMX = trimethoprim-sulfamethoxazole.

To the List, We Add

Tranexamic acid
Clarithromycin
Cefepime
Tramadol
Baclofen
Low molecular weight heparin

Support System



Bhardwaja B, Carroll NM, Raebel MA, Chester EA, Korner EJ, Rocho BE, Brand DW, Magid DJ. Improving prescribing safety in patients with renal insufficiency in the ambulatory setting: the Drug Renal Alert Pharmacy (DRAP) Program. Pharmacotherapy 2011;31:346-356.

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 ($p = 0.009$)

Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA 2001;286:2839-2844.

Stepwise Approach

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

Gary R. Matzke[1], George R. Aronoff[2], Arthur J. Atkinson Jr[3], William M. Bennett[4], Brian S. Decker[5], Kai-Uwe Eckardt[6], Thomas Golper[7], Darren W. Grabe[8], Bertram Kasiske[9], Frieder Keller[10], Jan T. Kielstein[11], Ravindra Mehta[12], Bruce A. Mueller[13], Deborah A. Pasko[14], Franz Schaefer[15], Domenic A. Sica[16], Lesley A. Inker[17], Jason G. Umans[18] and Patrick Murray[19]

Table 3 | Stepwise approach to adjust drug dosage regimens for patients with CKD and AKI

Step 1	Obtain history and relevant demographic/clinical information	Assess demographic information, past medical history including history of renal disease, and current clinical and laboratory information, including DNA polymorphisms to ascertain drug therapy needs
Step 2	Estimate GFR	Use most appropriate tool to assess eGFR or CL_{cr} for the patient based on age, body size, ethnicity, and concomitant disease states
Step 3	Review current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Calculate individualized treatment regimen	Determine treatment goals (see text); calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's volume status and eGFR or CL_{cr}
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CL_{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)

Wanner C et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238-248

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

Fellström BC et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395-1407

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

National Kidney Foundation®
KDOQI

KDOQI CLINICAL PRACTICE GUIDELINE FOR DIABETES AND CKD: 2012 UPDATE

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 sulphonyluea

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

Oral sulphonylurea

Second generation sulphonylurea

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

Table 4. Dose Adjustment for Insulin Compounds and Oral Medicines for Diabetes in CKD

Medication Class and Agents	CKD stages 3, 4, and 5 ND
Insulin	
Glargine	No advised dose adjustment*
Detemir	No advised dose adjustment*
Neutral Protamine Hagedorn (NPH)	No advised dose adjustment*
Regular	No advised dose adjustment*
Aspart	No advised dose adjustment*
Lispro	No advised dose adjustment*
Glulisine	No advised dose adjustment*
First-generation sulfonylureas	
Acetohexamide*†	Avoid use
Chlorpropamide	GFR 50-80 mL/min/1.73 m²: reduce dose 50%, GFR <50 mL/min/1.73 m²: avoid use
Tolazamide	Avoid use
Tolbutamide	Avoid use
Second-generation sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide*†	No dose adjustment
Meglitinides	
Repaglinide	If GFR <30 mL/min/1.73 m² start conservatively at 0.5 mg with meals
Nateglinide	If GFR <30 mL/min/1.73 m² start conservatively at 60 mg with meals
Biguanides	
Metformin*†‡	United States FDA label states, "do not use if SCr ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m²
Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
Alpha-glucosidase inhibitors	
Acarbose	Avoid if GFR <30 mL/min/1.73 m²
Miglitol	Avoid if GFR <25 mL/min/1.73 m²
DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m²: 100 mg daily GFR 30-50 mL/min/1.73 m²: 50 mg daily GFR <30 mL/min/1.73 m²: 25 mg daily
Saxagliptin	GFR >50 mL/min/1.73 m²: 5 mg daily GFR ≤50 mL/min/1.73 m²: 2.5 mg daily
Linagliptin	No dose adjustment
Vildagliptin*†	GFR ≥50 mL/min/1.73 m²: 50 mg twice daily GFR <50 mL/min/1.73 m²: 50 mg daily
Incretin mimetic	
Exenatide	Not recommended in GFR <30 mL/min/1.73 m²
Liraglutide	Not recommended in GFR <60 mL/min/1.73 m²
Amylin analog	
Pramlintide	No dose adjustment and not recommended for patients with CKD stage 4 or greater
Dopamine receptor agonist	
Bromocriptine mesylate*	Not studied in patients with reduced GFR

Metformin

- Most authorities have recommended a GFR cut-off of < 60 ml/min/1.73 m^2
- Too restricted use of metformin?

Metformin – cleared by kidney

- Clearance of metformin decreases by ~75% when GFR < 60 ml/min/1.73 m^2
- No further change when GFR declines to 30 ml/min/1.73 m^2
- At GFR 30-60 ml/min/1.73 m^2: serum concentration of metformin only two-fold higher than in normal kidney function

Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. J Clin Pharmacol 1995;35:1094-1102

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)

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;14:CD002967

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

Ekström N, Shiöer L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2:e001076

Metformin

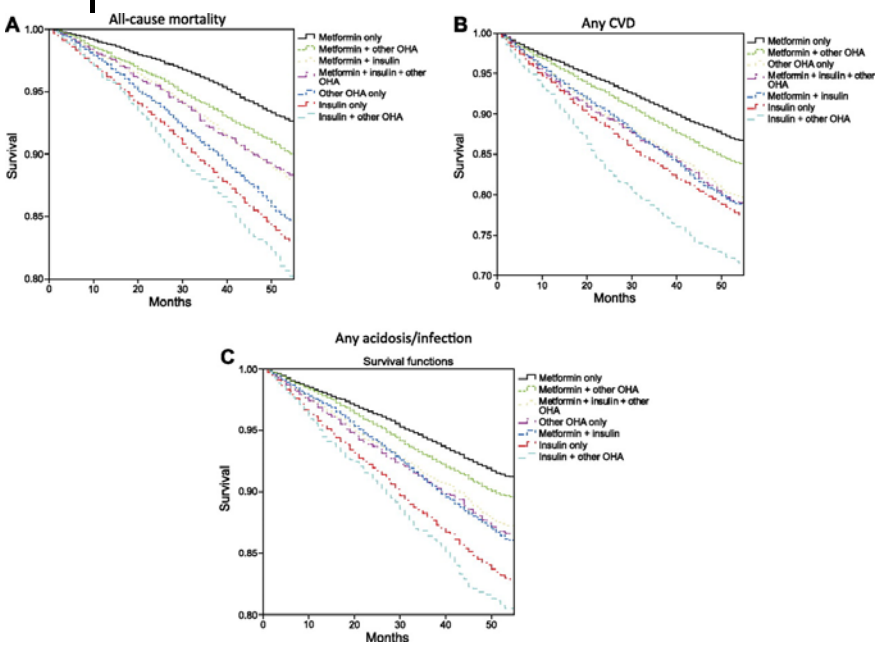
- Metformin associated with
  - reduced risk of CVD, acidosis/serious infection and all-cause mortality compared with insulin
  - reduced risk of all-cause mortality compared with other oral hypoglycaemic agents

Ekström N, Shiöer L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2:e001076

Large cohort study

- Effects consistent in patients with renal impairment (eGFR 45-60 ml/min/1.73 m^2)
- And no increased risk of acidosis/serious infection even in patients with low renal function (eGFR 30-60 ml/min/1.73 m^2)

Ekström N, Shiöer L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2:e001076



New recommendation

- Metformin use re-evaluated when GFR < 45 ml/min/1.73 m^2
- Stopped when GFR < 30 ml/min/1.73 m^2
- 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
Frusemide 250 mg daily
Ferrous sulphate 300 mg daily
Prazosin 0.5 mg nocte

Alfacalcidol

Vitamin D analogs (1α-hydroxyvitamin D_3) used to treat secondary hyperparathyroidism

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

Chagnac A, Ori Y, Weinstein T, Zevin D, Korzets A, Hirsh J, Edelstein S, Gafter U. Hypercalcemia during pulse vitamin D3 therapy in CAPD patients treated with low calcium dialysate: the role of the decreasing serum parathyroid hormone level. J Am Soc Nephrol 1997;8:1579-1586.

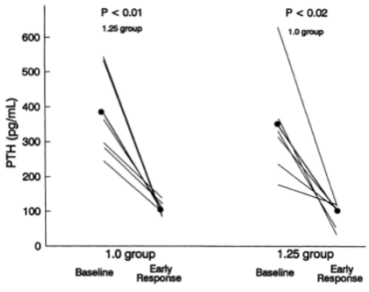


Figure 1. Serum PTH in 12 responders at baseline and early response.

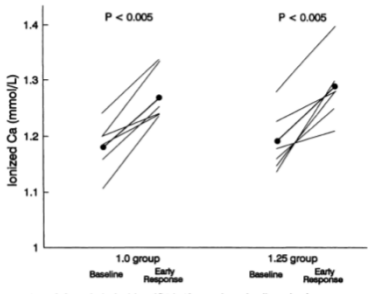


Figure 2. Serum ionized calcium (iCa) in 12 responders at baseline and early response.

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

MEDICATION ERRORS

Erroneous Dosing of Oral Methotrexate

Matthew Grissinger, RPh, FASCP

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 Chun Szeto, FRCP, MD,* Morris Hok Leung Tai, FRCPA,† Bonnie Ching Ha Kwan, MRCP,* and Philip Kam Tao 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 Pancytopenia

Patient	1	2	3	5	6	7
Author	Ellman et al[4]	Ellman et al[4]	Nakamura et al[5]	Chatham et al[9]	Chatham et al[9]	Chatham et al[9]
Country	USA	USA	Japan	USA	USA	USA
Age	52	47	57	49	52	61
Sex	Female	Female	Male	Male	Male	Female
Dialysis	HD	HD	HD	HD	HD	HD
Underlying disease(s)	Rheumatoid arthritis	Systemic sclerosis, polymyositis	Rheumatoid arthritis	Myositis	Myositis	Psoriasis with skin rash and arthropathy
Concomitant medications of relevance	Prednisone	Prednisone	NSAIDs	Prednisone	Folic acid	Nil
Methotrexate dosage (mg)	2.5 mg single dose	2.5 mg single dose	5 mg single dose	Two weekly doses	5 mg/wk	7.5 mg total dose (2.5 mg first week, 5 mg second week)
Clinical manifestations post-MTX	Fever, stomatitis, pharyngitis, rash	Fever, pneumonitis	Fever, stomatitis, fatigue, sepsis, jaundice	Fever, pharyngitis, oral mucositis	Sepsis, pneumonia	Sore throat, fever, sepsis, hypotension
Serum MTX level μmol/L	0.13	N/A	0.03	N/A	N/A	N/A
Management of MTX	Folinic acid, antibiotics	Antibiotics, hemodialysis	Antibiotics, transfusion of	Antibiotics, folinic acid	Antibiotics	Intubation, erythropoietin
Methotrexate toxicity	Charcoal emoperfusion	—	RBC and platelets, granulocyte colony stimulating factor, plasmapheresis	—	—	Granulocyte colony-stimulating factor, platelet transfusion
The lowest WBC	WBC: 0.5	WBC: 1.5	WBC: 0.1	WBC: 0.09	WBC: 2.2	WCC: 0.05
Clinical outcome	Death	Recovery	Recovery	Recovery	Recovery	Death
Autopsy	Yes	—	—	—	—	Yes

HD indicates hemodialysis; RBC, red blood cell; rHuEPO, recombinant human erythropoietin; WBC, white blood count $\times 10^9$/L; N/A, not available.

Methotrexate and renal failure

TABLE 1. (*Continued*)

8	9	10	11	12	13	14
Boulanger et al[6]	Basile et al[7]	Yang et al[8]	Hanna et al, 2006	Diskin et al[11]	Boey et al[12]	Our case
France	Italy	Taiwan	USA	USA	Belgium	Hong Kong
60	74	55	Young	60	66	56
Female	Female	Female	Female	Male	Male	Male
HD	HD	HD	HD	CAPD	HD	HD
Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis	Ectopic pregnancy	Arthritis	Psoriatic arthropathy	Psoriatic arthropathy
Steroids	Steroids	Prednisolone, celecoxib, sulfasalazine, folic acid	Nil	Nil	Folic acid	Mefenamic acid
5 mg/wk for 2 wk	5 mg/wk for 2 wk	7.5 mg/wk for 12 wk	50 mg/m^2	10 mg/wk for 2 wk	5 mg/wk for 2 wk	2.5 mg single dose
Stomatitis, diarrhea	Fever, stomatitis	Fever, stomatitis, fatigue, rash, bruising, carbuncles	Multiorgan failure	Nausea, hematemesis, odynophagia	Toxic erythroderma, oral mucositis, buccal ulceration, hepatomegaly, esophageal candidiasis	Fever, jaundice
N/A	N/A	N/A	0.11	0.53 down to 0.17 after treatment	0.03	0.06
Calcium folinic acid	Antibiotics, transfusion of	Antibiotics, antifungal	Folinic acid, antibiotics	Antibiotics, folinic acid	Folinic acid, hemodialysis	Antibiotics, hemodialysis
Hemodialysis with high-flux membrane without charcoal column	RBC and platelets, rHuEPO, standard bicarbonate hemodialysis, folinic acid	Therapy, transfusion of RBC and platelets, folic acid	Granulocyte colony stimulating factor	Rescue, recombinant human granulocyte colony stimulating factor, peritoneal dialysis, hemodialysis	Fluconazole, nystatin, granulocyte colony-stimulating factor, platelet and red blood cells transfusion, antibiotics	—
WBC: 1.3	WBC: 1.7	WBC: 0.63	WBC: 0.4	WBC: 0.3	Neutrophil: 0.07	WBC: 0.06
Recovery	Recovery	Recovery	Death	Death	Recovery	Death
—	—	—	Yes	—	—	Yes

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)

Haemodialysis

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

Haemodialysis

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)

Haemodialysis

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)

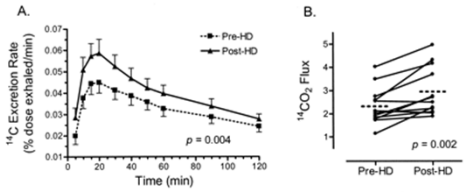
Haemodialysis

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



Nolin TD, Appiah K, Kendrick SA, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. J Am Soc Nephrol 2006;17:2363-2367.

Example of erythromycin

Mechanism proposed

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

Nolin TD, Appiah K, Kendrick SA, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. J Am Soc Nephrol 2006;17:2363-2367.

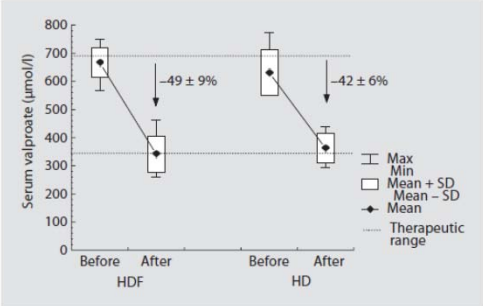
Steps We can Take

- 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)

Gubensek J, Buturovic-Ponikvar J, Ponikvar R, Cebular B. Hemodiafiltration and high-flux hemodialysis significantly reduce serum valproate levels inducing epileptic seizures: case report. Blood Purif 2008;26:379-380.

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/m^2)

Type of complication	Tacrolimus group	Sirolimus group	*P* value[a]
Perigraft fluid collection	2	9	0.038
Superficial wound infection	1	11	0.004
Incisional hernia	0	8	0.005
Superficial wound dehiscence	0	4	0.051
Cellulitis	2	4	0.462
Seroma	0	1	0.335
Fascial dehiscence	1	4	0.201
Deep wound infection	0	2	0.171
Urinary leak	0	2	0.171
Total	6	45	<0.001

[a] 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

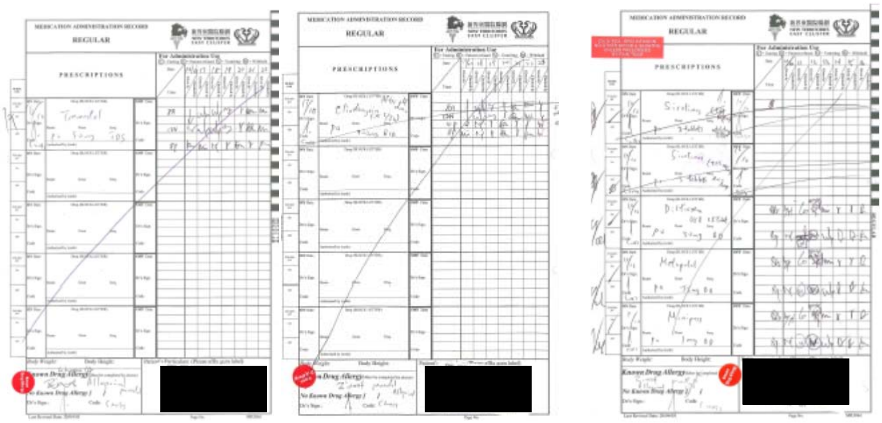
Tramadol, pregabalin, cyclosporine, prednisolone, lactulose, Bisolvon, colchicine, clindamycin, metoprolol, prazosin, diltiazem

Medical review

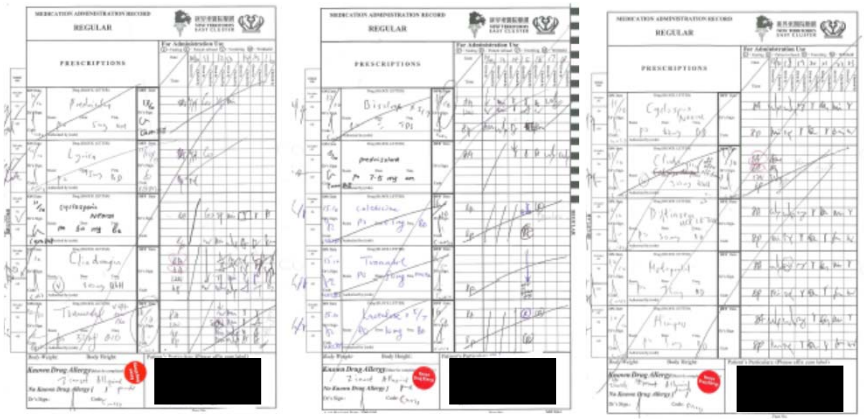
Found out that patient was not on prednisolone for 6 days

(because of missed renewal when transcribing the medications by intern)

Six pages of drug charts



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 CYP3A, According to Drug Class.*

CYP3A Substrates	CYP3A Inhibitors	CYP3A Inducers
Calcium-channel blockers	Calcium-channel blockers	Rifamycins
Diltiazem	Diltiazem	Rifabutin
Felodipine	Verapamil	Rifampin
Nifedipine	Azole antifungal agents	Rifapentine
Verapamil	Itraconazole	Anticonvulsant agents
Immunosuppressant agents	Ketoconazole	Carbamazepine
Cyclosporine	Macrolide antibiotics	Phenobarbital
Tacrolimus	Clarithromycin	Phenytoin
Benzodiazepines	Erythromycin	Anti-HIV agents
Alprazolam	Troleandomycin	Efavirenz
Midazolam	(Not azithromycin)	Nevirapine
Triazolam	Anti-HIV agents	Others
Statins	Delavirdine	St. John's wort
Atorvastatin	Indinavir	
Lovastatin	Ritonavir	
(Not pravastatin)	Saquinavir	
Macrolide antibiotics	Others	
Clarithromycin	Grapefruit juice	
Erythromycin	Mifepristone	
Anti-HIV agents	Nefazodone	
Indinavir		
Nelfinavir		
Ritonavir		
Saquinavir		
Others		
Losartan		
Sildenafil		

* These inhibitors and inducers can interact with any CYP3A substrate and may have important clinical consequences. HIV denotes human immunodeficiency virus.

Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211-2221.

Risk of graft rejection

Sub-therapeutic cyclosporine level

Not to mention… the inadvertent discontinuation of prednisolone…

Take Home Message

Clinical Pearls

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

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

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