# Drug Therapy in Patients with Chronic Kidney Disease (CKD)

Yacoub Irshaid, MD, PhD, ABCP

# Drug Therapy in Patients with CKD

- **Individualization of a drug dosage regimen for a patient with reduced kidney function is based on:**

1. **The pharmacodynamics/pharmacokinetics of the drug.**
2. **Residual renal function.**
3. **The overall clinical condition of the patient.**

# Drug Therapy in Patients with CKD

- **In addition to the decrease in renal clearance, non-renal clearance (gastrointestinal and hepatic drug metabolism) of several drugs is also reduced.**

| GFR Category | GFR (mL/min/1.73 $m^2$) | Renal dysfunction |
|---|---|---|
| 1 | >90 | Normal function |
| 2 | 60–89 | Mild |
| 3a | 45–59 | Mild- to -moderate |
| 3b | 30–44 | Moderate- to - severe |
| 4 | 15–29 | Severe |
| 5 | <15 | Renal failure |

# Drug Therapy in Patients with CKD

- **Medications which are predominantly eliminated unchanged by the kidney may accumulate in CKD patients, leading to an increase the risk of adverse effects.**
- **If 30% or more of a drug is eliminated unchanged in the urine, it may require dosage adjustment in CKD patients, especially in those with stage 3 - 5 disease.**

# Drug Therapy in Patients with CKD

- **Changes in protein binding, altered cytochrome P450 enzyme activity, and altered trans-cellular transport systems that are associated with CKD may affect serum and tissue drug concentrations and necessitate drug dosing adjustments.**

# Drug Therapy in Patients with CKD

- **The dosage of many drugs must be altered to prevent toxicity, without compromising the achievement of the desired therapeutic outcome.**
- **Dangerous dosing errors in CKD patients still occur.**

# Pharmacokinetic Changes In CKD

## Drug Absorption:

- **The absorption and bioavailability of some drugs is highly variable in CKD patients.**
- **The mechanisms responsible are multifactorial and include; drug interactions, delayed gastric emptying, and reduced gastric acidity.**
- **Decreased gastrointestinal (GI) motility secondary to gastroparesis in patients with diabetes may delay the $t_{max}$ (time to peak)and may also reduce the $C_{max}$ (peak concentration).**

# Pharmacokinetic Changes In CKD

- If a drug undergoes GI metabolism, the slower transit time allows for more GI metabolism and thus lower $C_{max}$ of the parent drug.
- Urea retention in CKD patients results in a high influx of urea into the gut, which is converted to ammonia, leading to an increase in gastric pH.
- The increase in gastric pH may alter the dissolution or ionization properties of weakly basic drugs leading to changes in absorption.

# Pharmacokinetic Changes In CKD

- **A reduction in gastric acidity, associated with the concomitant administration of antacids, $H_2$-receptor antagonists, proton pump inhibitors, and phosphate binders reduce the bioavailability of several antibiotics and digoxin.**
- **Antacids and multivitamin supplements may decrease the bioavailability of some drugs as a result of the formation of insoluble salts or metal ion chelates.**

# Pharmacokinetic Changes In CKD

- **Edema of the GI tract, secondary to cirrhosis or congestive heart failure in CKD patients, can decrease the absorption of some drugs (reduce oral absorption of furosemide from 10 – 50%).**
- **The bioavailablity of only a few drugs (dextropropoxyphene, dihydrocodeine, felodipine, sertraline, and cyclosporine) increases in CKD patients.**
- **This is due to reduction in first-pass metabolism.**

# Pharmacokinetic Changes In CKD

- **Drug interactions may independently alter bioavailability.**
- **Bioflavonoids in grapefruit juice inhibit CYP3A4 enzyme and noncompetitively inhibit the metabolism of drugs metabolized by this enzyme.**
- **This interaction can increase the bioavailability of cyclosporine by as much as 20%.**

# Pharmacokinetic Changes In CKD

**Distribution:**

- **The $V_D$ of many drugs may be increased in categories 3-5 CKD patients leading to a reduction in serum drug concentration.**
- **The increase in $V_D$ may be due to: fluid overload secondary to excessive fluid administration or intake, or decreased plasma protein binding.**

# Pharmacokinetic Changes In CKD

- **Decreased tissue binding of drugs in CKD patients may result in a reduction in $V_D$ (digoxin and pindolol).**
- **Variability in fluid status is common in patients with severe CKD (category 4 & 5), especially those that are critically ill.**

# Changes of Volume of Distribution of Selected Drugs in Patients with ESRD

| Increased $V_D$ | Decreased $V_D$ |
| --- | --- |
| Aminoglycosides, Cephalosporins, Dicloxacillin, Erythromycin, Furosemide, Isoniazide, Naproxen, Phenytoin, Trimethoprim, Vancomycin… | B-blockers, Ciprofloxacin, Digoxin, Ethambutol, Methicillin… |

# Pharmacokinetic Changes In CKD

- **Many critically ill patients receive large volumes of IV fluids, and can subsequently develop edema, pleural effusions, or ascites.**
- **These, in addition to reduced water excretion in CKD, may lead to an increase the $V_D$ of water-soluble drugs and decrease their serum concentration (aminoglycosides and cephalosporins $V_D$ may be increased by up to 150%).**

# Pharmacokinetic Changes In CKD

## Effect of Altered Plasma Protein Binding:

- **Many drugs have altered protein binding in CKD patients.**
- **Protein binding of many acidic drugs is reduced (penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin) secondary to:**

# Pharmacokinetic Changes In CKD

1. **Hypoalbuminemia.**
2. **Qualitative changes in the conformation of the protein binding site.**
3. **Competition for binding sites by other drugs, metabolites, and endogenous waste products than accumulate in renal dysfunction.**

# Pharmacokinetic Changes In CKD

- **Protein binding of phenytoin (90% protein-bound, primarily to albumin) is significantly reduced secondary to decreased plasma phenytoin binding affinity for albumin, as well as low serum albumin, leading to an increase in the unbound concentration.**
- **These changes alter the relationship between total phenytoin concentration and desired or toxic effects.**

# Pharmacokinetic Changes In CKD

- **The increase in unbound fraction, from 10% in normal renal function to 20% or more in category 5 CKD, results in increased hepatic clearance and decreased total concentrations.**
- **Thus, the therapeutic range based on total phenytoin concentration is shifted downward from 10-20 mg/L to values as low as 4-8 mg/L.**
- **However, the unbound concentration range remains the same for all patients (normal or CKD).**

# Pharmacokinetic Changes In CKD

- **One can approximate the total phenytoin concentration that would be observed in category 5 CKD patients if they had normal plasma protein binding ($C_{\text{normal binding}}$).**
- **For albumin expressed in g/L the equation is:**

$$C_{\text{total normal binding}} = C_{\text{total reported}} / [(0.9)(0.48)\ (\text{albumin}/44)] + 0.1$$

# Pharmacokinetic Changes In CKD

- **The principal binding protein for several basic drugs is $\alpha_1$-acid glycoprotein, an acute-phase reactant protein, whose plasma concentrations are increased in CKD patients.**
- **As a result, the unbound fraction of some basic drugs (disopyramide) may be significantly decreased in CKD patients.**

# Pharmacokinetic Changes In CKD

## Effect of Altered Tissue Binding:

- Few drugs (pindolol, ethambutol, and digoxin) are affected.
- Tissue binding is reduced and the $V_D$ of digoxin is decreased by 50% in patients with category 5 CKD, leading to elevated serum concentrations.
- In this case, the absolute amount of digoxin bound to the receptor is reduced.

# Pharmacokinetic Changes In CKD

**Elimination:**

- **Elimination of a drug from the body is expressed as total systemic clearance ($CL_T$), which is defined as the sum of renal clearance ($CL_R$) and non-renal clearance $CL_{NR}$.**
- **Remember that total clearance does NOT only reflect drug elimination. It is also affected by drug distriburion ($CL_T = K.V_D$).**

# Pharmacokinetic Changes In CKD

## Non-renal Clearance:

- $CL_{NR}$ refers to all routes of drug elimination, except renal excretion of unchanged drug.
- It includes hepatic and extrahepatic metabolism and transcellular transport pathways.
- It might be affected by renal disease.

# Pharmacokinetic Changes In CKD

## Accumulation of Metabolites:

- **Drugs that are eliminated by glomerular filtration, and given to category 4 & 5 CKD patients may have significant accumulation of parent drug and its metabolite(s).**
- **The accumulation of metabolites and toxic end-products of intermediary metabolism seen in CKD, may affect the disposition of other drugs.**

# Pharmacokinetic Changes In CKD

- **Some metabolites may have pharmacologic activity similar to that of the parent drug:**

a. **Oxypurinol is an active metabolite of allopurinol**

b. **Morphine is metabolized to the active metabolites morphine-3- glucuronide and morphine-6-glucuronide which readily cross the blood-brain barrier and bind to opiate receptors, exerting strong analgesic effects.**

# Pharmacokinetic Changes In CKD

- **The metabolite may have dissimilar pharmacologic action (norpethidine has CNS stimulatory activity that produces seizures, whereas pethidine has CNS depressant actions).**

# Pharmacodynamic Changes In CKD

- **In CKD, the response to a given drug many change beyond that predicted by pharmacokinetic changes alone.**
- **For example, uremic toxins' accumulation may cause complex disturbances of the coagulation system leading to increased bleeding.**
- **Therefore, enoxaparin dosage adjustment based on creatinine clearance may NOT lead to optimal anticoagulation.**

# Estimation of Kidney Function for Drug Dosage Regimen Individualization

- **Accurate assessment of kidney function is needed for appropriate drug dosing regimens.**

**Methods:**

1. **Accurate measurement of GFR (creatinine clearance) as you see in the clinical setting.**
2. **Use of equations derived by epidemiological studies. Many of these are available for different populations of patients.**

# Estimation of Kidney Function for Drug Dosage Regimen Individualization

- You should be aware that these equations are only approximations, and other patient factors should be considered.
- Then, the maintenance dose (MD) can be calculated according to renal clearance taking into consideration the presence of non-renal clearance of the drug.

$$MD = Cl_T \times \text{Desired } C_{ss}$$

# Relationship Between $CL_{cr}$ and CL of Select Drugs

| Drug | Total Body Clearance |
|---|---|
| Amikacin | CL = 0.6 (CLcr) + 9.6 |
| Gentamicin | CL = 0.983 (CLcr) |
| Ciprofloxacin | CL = 2.83 (CLcr) + 363 |
| Digoxin | CL = 0.88 (CLcr) + 23 |
| Imipenem | CL = 1.42 (CLcr) + 54 |
| Lithium | CL = 0.20 (CLcr) |
| Piperacillin | CL = 1.36 (CLcr) + 1.50 |
| Vancomycin | CL = 0.69 (CLcr) + 3.7 |

# References for Drug Dosing in CKD


1. Aronoff's Drug Prescribing in Renal Failure.
2. The Renal Drug Handbook.
3. Lexicomp.
4. Micromedex.
5. American Hospital Formulary Service.

# Dosing Adjustments

**Methods for maintenance dosing adjustments:**

- **Dose reduction, lengthening the dosing interval, or both.**

1. **Dose reduction involves reducing each dose while maintaining the normal dosing interval.**

- **This approach maintains more constant drug concentrations, but is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination.**

# Dosing Adjustments

2. **Normal doses are maintained, but the dosing interval is prolonged to allow time for drug elimination before re-dosing.**

- **Prolongation of the dosing interval is associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval.**

# Dosing Adjustments

1. **Diuretics:**

- **Thiazide diuretics are considered first-line treatment for patients with uncomplicated hypertension and CKD (only if Scr < 2.5 mg/dL or CrCl > 30 mL/min).**
- **Loop diuretics are also commonly used to treat uncomplicated hypertension in CKD patients.**
- **Potassium-sparing diuretics should be avoided because potassium is dangerous to these patients.**

# Dosing Adjustments

2. **Antihypertensives:**

- **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are first-line antihypertensives used in patients with type 1 or 2 diabetes and early CKD.**
- **Hydrophilic β-blockers (atenolol, bisoprolol, and nadolol) require dosing adjustments in CKD patients.**

# Dosing Adjustments

3. **Antihyperglycemic Agents:**

- **A renally-excreted agent like metformin is not recommended if Scr is >1.5 mg/dL in men or >1.4 mg/dL in women.**
- **It is important to monitor CKD patients on metformin closely for lactic acidosis development.**
- **Sulfonylureas (chlorpropamide and glyburide) should be avoided in patients with stage 3 - 5 CKD, as their use increases hypoglycemia risk.**

# Dosing Adjustments

4. **Analgesics:**

- **Metabolites of morphine, tramadol, and codeine can accumulate in CKD patients, leading to respiratory depression.**
- **Dosage reduction is recommended for morphine and codeine in patients with CrCl < 50 mL/min.**
- **Metabolite accumulation can lead to supra-therapeutic concentrations and cause toxicity.**
- **Dosing intervals for opioids may need to be modified in CKD patients.**

# Dosing Adjustments

5. **Statins:**

- **Statin therapy for dyslipidemia is commonly used in CKD patients.**

a. **Atorvastatin has NO dose adjustment recommendation.**

b. **Rosuvastatin, simvastatin, and lovastatin need dose adjustment**

c. **Fluvastatin should be used with caution in CKD patients.**

# Dosing Adjustments

- **The following slides might be used as resource information for dose adjustment in CKD.**

# Dosing Requirements of Select Drugs in Patients with Chronic Kidney Disease

| Drug | Usual Dose | Percent of usual dose | |
|---|---|---|---|
| | | GFR 10-50 | GFR < 10 |
| **ACE-inhibitors** | | | |
| Enalapril | 5-10 mg q12 hours | 50-100% | 50% |
| Lisinopril | 5-10 mg daily | 50-75% | 25-50% |
| **β-Blockers** | | | |
| Atenolol | 50-100 mg daily | 50% | 25% |
| Bisoprolol | 10 mg daily | 75% | 50% |
| **Diuretics** | | | |
| Amiloride | 5 mg daily | 50% | Avoid |
| Spironolactone | 50-100 mg daily | 10 mg daily max (watch for hyperkalemia) | Avoid |
| Furosemide & bumetanide | | No adjustment needed | |
| Thiazide | 25-50 mg daily | 100% | Avoid |
| Triamterene | 50-100 mg twice daily | 100% (watch for hyperkalemia) | Avoid |

| Antidiabetic drugs | | | |
|---|---|---|---|
| Glipizide | 5 mg daily | No dose adjustment needed | |
| Glyburide | 2.5-5 mg daily | Avoid | Avoid |
| Metformin | | Monitor for lactic acidosis)<br>Avoid if $Cr_{sr}$ > 1.5 mg/dl in males or > 1.4 mg/dl in females, patients older than 80 years with chronic heart failure.<br>It should be temporarily discontinued for 24-48 hours before use of iodinated contrast media, and restarted for 48 hours afterward.<br>May be started only when renal function has normalized. | |

| Antifungals | | | |
|---|---|---|---|
| Fluconazole | 200-400 mg daily | 50% | 50% |
| Itraconazole | 100-200 mg q 12 hours | 100% | 50% (IV form contraindicated) |
| Miconazole | | No adjustment needed | |

| Antibiotics | | | |
|---|---|---|---|
| Imipenem | 0.25-1 g q 6 hours | 50% | 25% |
| Meropenem | 1-2 g q 8 hours | 50% q 12 hours | 50% q 24 hours |
| Cefazolin | 0.25-2 g q 6 hours | 0.25-2 g q 12 hours | 50% q 24-48 hours |
| Cefepime | 0.25-2 g q 8-12 hours | 50-100% q 24 hours | 25-50% q 24 hours |
| Cefixime | 200 mg q 12 hours | 75% | 50% |
| Cefotaxime | 1-2 g q 6-12 hours | q 6-12 | 50% |
| Cefotetan | 1-2 g q 12 hours | q 24 hours | q 48 hours |
| Ceftazidime | 1-2 g q 8 hours | q 12-24 hours | q 24-48 hours |
| Ceftriaxone | No adjustment needed | | |
| Cefuroxime | 0.75-1.5 g q 8 hours | q 8-12 hours | q 12 hours |
| Cephalexin | 250-500 mg q 6-8 hours | q 8-12 hours | Q 12-24 hours |
| Clarithromycin | 250-500 mg q 12 hours | 50-100% | 50% |
| Penicillin G | 0.5-4 million U q 4-6 hours | 75% | 50% |

| | | | |
|---|---|---|---|
| Piperacillin/tazobactam | 3.375-4.5 g q 6-8 hours | 2.25-g q 6-8 hours | 2.25 g q 8 hours |
| Ticarcillin/clavulanate | 3.1g q 4 hours | q 8-12 hours | 2 g q 12 hours |
| Ciprofloxacin | 400 mg IV q 12 hours | 50-75% | 50% |
| | 500-750 mg orally q 12 hours | 50-75% | 50% |
| Gemifloxacin | 320 mg q 24 hours | 50-100% | 50% |
| Levofloxacin | 250-750 mg Q24 hours | 500-750 mg initial dose, then 250-750 mg Q 24-48 hours | 500 mg initial dose, then 250-500 mg Q 48 hours |
| Moxifloxacin | | No dose adjustment needed | |
| Sulfamethoxazole | 1 g q 8-12 hours | q 18 hours | q 24 hours |
| Trimethoprim | 100 mg q 12 hours | q 12-18 hours | q 24 hours |
| Doxycycline | | No dose adjustment needed | |
| Clindamycin | | No dose adjustment needed | |
| Nitrofurantoin | 500-1000 mg q 6 hours | Avoid | Avoid |

| Statins | | | |
|---|---|---|---|
| Atorvastatin | 10 mg daily | No dose adjustment needed | |
| Lovastatin | 20-40 mg daily | Use with caution when GFR <30 ml/min | |
| Rosuvastatin | 5-40 mg daily | 5 mg daily in patients with GFR <30 ml/min, no to exceed 10 mg | |
| Simvastatin | 10-20 mg daily | 5 mg daily in patients with GFR <10 ml/min. | |
| **Other drugs** | | | |
| Allopurinol | 300 mg daily | 50% | 25% |
| Famotidine | 20-40 mg at bedtime | 25% | 10% |
| Gabapentin | 300-600 mg q 8 hours | 400-1400 mg twice daily, when GFR > 30-59 ml/min.<br>200-700 mg daily when GFR > 15-29 ml/min. | 100-300 mg daily |
| Metoclopramide | 10-15 mg 3 times daily | 75% | 50% |