Drug Use in Patients with Renal Failure

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ABSTRACT

In general, dosage adjustment in RF is not required when (a) renal elimination of the drug is <33%, and the metabolites are not active, or (b) GFR is still > 50 mL/min, and for most antibiotics, when GFR is still > 20 mL/min. For drugs with narrow margin of safety and the main elimination is by renal excretion (e.g. aminoglycosides, vancomycin, digoxin), dosage adjustment is required in all degrees of RF. Drug dosage in RF can be estimated from calculation or dosing tables. Drug use in RF should be avoided if too risky (e.g. tetracycline) and other safer drugs are available. The dosage estimation should be refined by titration of efficacy and safety in individual patients. Supplemental dose post-HD is required when HD clearance is at least 30% of total body clearance. Predictably, this is for drugs with MW < 500 D, water soluble, uncharged, minimal protein binding, and Vd < 1 L/kg. Alteration in pharmacokinetics and pharmacodynamics of drugs in RF causes increased risk of adverse drug reactions. Multiple medications in patients with RF cause increased drug interactions in these patients.

Key words: renal failure, dosage adjustment, hemodialysis, Cockroft & Gault Formula, Giusti-Hayton correction factor

ABSTRAK

Umumnya, penyesuaian dosis pada gagal ginjal (GG) tidak diperlukan jika (a) eliminasi obat oleh ginjal <33%, dan metabolitnya tidak aktif, atau (b) laju filtrasinya > 50 mL/menit, dan untuk kebanyakan antibiotik, jika LFG masih > 20% mL/menit. Untuk obat-obat dengan batas keamanan yang sempit dan eliminasi utamanya melalui ginjal (misalnya aminoglikosida, vankomisin, digoksin), penyesuaian dosis diperlukan pada semua derajat gagal ginjal. Dosis obat pada GG dapat diestimasi dari perhitungan atau tabel dosis. Penggunaan obat pada GG harus dihindarkan jika terlalu berisiko (misalnya tetraksilin) dan ada obat-obat lain yang lebih aman. Estimasi dosis harus diperlakukan dengan titrasi efikasi dan keamanan pada masing-masing pasien. Dosis pengganti pasca-hemodialisis (HD) diperlukan jika kliens HD sedikitnya 30% dari kliens tubuh total. Hal ini dapat diprediksi untuk obat dengan berat molekul < 500 D, larut air, tidak bermuatan, ikatan protein minimal, dan Vd < 1 L/kg. Perubahan dalam farmakokinetik dan farmakodinamik obat pada GG meningkatkan risiko terjadinya efek samping. Banyaknya obat yang diberikan pada pasien GG meningkatkan terjadinya interaksi obat pada pasien GG ini. Arini Setiawati. Penggunaan Obat pada Pasien Gagal Ginjal.

Kata kunci: gagal ginjal, penyesuaian dosis, hemodialisis, formula Cockroft & Gault, faktor koreksi Giusti-Hayton

INTRODUCTION

Drugs are eliminated by hepatic metabolism to inactive metabolites and/or by renal excretion of parent drug and/or active or toxic metabolites.

In renal failure, for drugs eliminated completely or partially (more than 33%) by the kidneys, renally excreted active or toxic metabolites need dosage adjustment. Meanwhile, clinically significant removal by hemodialysis need a supplemental dose.

In renal failure (RF), drug pharmacokinetics and pharmacodynamics are frequently altered, resulting in increased risks of adverse drug reactions. Moreover, multiple medical problems in patients with RF lead to polypharmacy and consequently increased drug interactions.

PHARMACOKINETICS IN RENAL FAILURE

Absorption

Patients with renal failure experience nausea, vomiting, diarrhea and/or bowel edema, which cause drug malabsorption; it is worsened by nonsteroidal anti-inflammatory drugs (NSAIDs). Increased salivary urea in patients with renal failure, by gastric ureases will be converted to ammonia, which will increase gastric pH and cause decreased absorption of iron, ketoconazole, itraconazole and other drugs requiring acid medium for their absorption.

Distribution & protein binding

Uremia and increased plasma free fatty acids in patients with renal failure will cause decreased binding of acidic drugs to albumin, resulting in increased free drugs level in plasma. Increased plasma free drugs level will lead to increased intensity of drug effect, extent of drug distribution, and rate of drug elimination, and decreased total plasma concentration.

These effects are due to only free drugs can diffuse out of the capillary blood vessels to...
be distributed to the receptors where they act, and to the organs of elimination where they are eliminated, leading to decreased total plasma concentration. Edema or ascites in renal failure causes increased volume of distribution of water soluble drugs, while volume contraction decreases volume of distribution of aminoglycosides and increases its plasma concentration. Digoxin is accumulated in muscles, therefore muscle wasting in patients with renal failure causes a decrease in its volume of distribution and an increase in its plasma concentration.

**Metabolism**

For drugs that are metabolized completely by the liver to inactive metabolites, no dosage adjustment is required in patients with renal failure. Phase II metabolism or conjugation reactions are normal in renal failure. Among phase I reactions, the microsomal oxidation is normal or accelerated (due to accumulation of inducers). Meanwhile, reduction (e.g. cortisol), peptide hydrolysis (e.g. insulin, glucagon and PTH), and ester hydrolysis (e.g. diflunisal and procaine), are slowed due to decreased biliary excretion. Organic acids, such as conjugates and free fatty acids, accumulate in renal failure. They will inhibit secretion of other organic acids that are also secreted by proximal renal tubule because of competition for the same efflux transporter, P-glycoprotein. For example, the renal secretion of penicillins, cephalosporins, sulfonamides, nitrofurantoin, thiazides and furosemide is inhibited. The competition of organic bases is usually not clinically important.

Passive tubular reabsorption is only for nonionic lipid soluble drugs. It is affected by urinary flow rate and urinary pH. In renal failure, the urinary flow decreases, but the tubular concentrations of drugs also decrease, and hence the passive tubular reabsorption is not affected.

End-stage renal disease (ESRD) means glomerular filtration is diminished to almost none. In this situation, tubular secretion of acidic drugs is much decreased due to competition with high accumulation of organic acids, and therefore dialysis is required. Drugs excreted by glomerular filtration, are water soluble and hence at least partially dialyzable, while drugs excreted by tubular secretion are or are not dialyzable.

**Excretion**

Renal excretion consists of glomerular filtration, active tubular secretion, and active and passive tubular reabsorption. Examples of drugs mainly eliminated by renal excretion can be seen in Table 1. These drugs are excreted by the kidneys in unchanged form, and hence they will accumulate in renal failure, causing increased intensity of their pharmacological effects and toxicity; therefore their dosage should be reduced in renal failure.

**Table 1** Drugs mainly eliminated by renal excretion
- Nitrofurantoin
- Penicillins
- Cephalosporins
- Aminoglycosides
- Diuretics
- Tetracyclines (Avoid !)
- Sulfonylunides
- ACE inhibitors
- Digoxin
- Ethambutol
- Atenolol
- Disopyramide

Only unbound drugs with molecular weight less than 60,000 Dalton are filtered by functional nephrons. In renal failure, the functional nephron mass decreases, causing a decrease in glomerular filtration. For example, ampicillin, aminoglycosides, and digoxin are excreted mainly by glomerular filtration. Ampicillin has a large margin of safety, and decreased glomerular filtration is compensated by increased biliary excretion, therefore a decrease in dosage is required only when the GFR is less than 20 mL per minute. On the other hand, aminoglycosides and digoxin have low therapeutic ratios, and therefore their dosage should be decreased in all degrees of renal failure. Dysfunction of tubular secretion will cause a decrease in excretion of drugs actively secreted by proximal renal tubule. Organic acids, such as conjugates and free fatty acids, accumulate in renal failure. They will inhibit secretion of other organic acids that are also secreted by proximal renal tubule because of competition for the same efflux transporter, P-glycoprotein. For example, the renal secretion of penicillins, cephalosporins, sulfonamides, nitrofurantoin, thiazides and furosemide is inhibited. The competition of organic bases is usually not clinically important.

Supplemental dose after HD is required if significant drug removal occurs during HD. Drugs with MW less than 500 Dalton, that are water soluble and unchanged, having minimal protein binding and volume of distribution less than 1 L/kg, undergo significant removal.

HD clearance is clinically significant if it increases total body clearance by 30 to 50%. Since dose is plasma concentration times volume of distribution (\(V_d\)), then

Supplemental dose = \(\text{desired concentration} - \text{concentration post HD} \times V_d\)

Peritoneal dialysis (PD) is very inefficient in removing drugs, e.g. 1 HD treatment can remove 2/3 of body stores of aminoglycosides, while 24-hour CAPD (continuous ambulatory peritoneal dialysis) removes only 25 – 30% of the drug.

**Table 2** Drugs requiring supplemental doses after each HD session
- Aminoglycosides
- Cephalosporins (most)
- Penicillins (most)
- Sulfonamides, TMP
- Ofloxacin, Ciprofloxacin
- Metronidazole
- Fluocytosine
- Ethambutol, INH
- Pyrazinamide
- Aciclovir, Ganciclovir
- Zidovudine, Didanosine

**Dosage Adjustment in Renal Failure**

Drug elimination by the kidney is assumed to be directly proportional to GFR (glomerular filtration rate), and \(C_{cr}\) (creatinine clearance) is traditionally used to approximate GFR. Cockcroft & Gault formula calculates \(C_{cr}\) from \(C_{cr}\) (creatinine plasma concentration).

For men: \(C_{cr} (\text{ml/min}) = \frac{(140 - \text{age}) \times \text{ideal BW (kg)}}{72 \times C_{cr} (\text{mg/dl})}\)

For women: \(0.85 \times C_{cr}\) for men
For acute renal failure, \( Cl_{\text{FR}} < 10 \text{ mL/min} \) should be assumed for drug dosage adjustment.

**Loading dose (\( D_L \))**  
\( D_L \) is given to achieve therapeutic concentration directly  
\[ D_L = \text{Desired therapeutic conc. (peak)} \times V_j \]  
\( (\text{mg/kg}) \) \( (\text{mg/L}) \) \( (\text{L/kg}) \)

No adjustment are needed for \( D_L \) in renal failure, except for digoxin, 50 – 75% of the usual \( D_L \) and aminoglycosides, 75 – 80% of the usual dose, because of decreased \( V_j \) and narrow margin of safety.

**Maintenance dose (\( D_M \))**  
Dosage adjustment is required for \( D_M \) in renal failure. There are 2 methods for this purpose. The first method is interval extension (I) with normal \( D_M \). This method may produce odd interval and hence causing increased dosing errors and decreased compliance. This method is not for drugs with narrow margin of safety because of large plasma level fluctuation, but it is encouraged for drugs with concentration-dependent killing (e.g. aminoglycosides). The second method is \( D_M \) reduction (D) with normal interval. This method is desired for drugs with narrow margin of safety (e.g. digitals, antiarrhythmics, tricyclic antidepressants, anticonvulsants), and is not for drugs which stable plasma concentrations are not desired (e.g. due to toxicity from aminoglycosides). A combination of I and D methods can be used for convenience, provided efficacy and safety are not jeopardized. The following formula are used for calculation of maintenance dose adjustment:

\[ G = 1 \times f \times \frac{1}{1 - \text{GFR/GFR}^N} \]

where:

- \( G \) = Giusti-Hayton correction factor
- \( \text{GFR} \) = GFR in renal failure
- \( \text{GFR}^N \) = normal GFR
- \( Cl_{\text{FR}} \) = renal clearance of the drug
- \( Cl_{\text{N}} \) = total clearance of the drug

\[ D_M = D_L \times G \]  
\( f = \frac{D_M}{D_L} \times \text{GFR}^N \)

where:

- \( D_M \) = \( D_M \) in renal failure
- \( D_L \) = normal \( D_L \)
- \( \text{GFR}^N \) = normal \( \text{GFR} \)
- \( f \) = normal \( f \)

For small \( \text{GFR} \) in ESRD (\( Cl_{\text{FR}} < 10 \text{ mL/min} \)), use \( Cl_{\text{insulin}} \) (inulin clearance) or \( Cl_{\text{inhemod}} \) (not \( Cl_{\text{FR}} \)) because some creatinine is secreted via the renal tubule.

**Example** of maintenance dose adjustment:  
Drug A has \( f = 1 \), meaning that all of the drug is excreted unchanged via the kidney (\( Cl_{\text{FR}} = Cl_{\text{FR}} \)).

Renal failure with \( \text{GFR} = 33 \text{ mL/min} \), normal \( \text{GFR} = 100 \text{ mL/min} \).

Normal dosage = 7 mg/kg once daily in 60 kg patient.

\[ G = 1 - 1 (1 - 33/100) = 1/3 \]

\( D_M \) in renal failure:

- 7 x 60 mg = 420 mg every 1/G = 3 days or
- 420 mg x 1/G = 420 mg x 1/3 = 140 mg once daily or
- 2/3 x 420 mg = 280 mg every 2 x 1 day = 2 days

Among these 3 dosages, choose the most convenient one.

**Pharmacodynamics in Renal Failure**  
In renal failure, many changes in homeostatic mechanism occur, resulting in changes in responses to drugs.

These changes are among others:

1. hyperkalemia, commonly occurs in renal failure, will increase myocardial irritability to catecholamines which may cause cardiac arrhythmias
2. hypokalemia, may also occur due to low potassium diet, diuretic use or some renal diseases, will increase myocardial sensitivity to digitals toxicity
3. uremia will cause:
   - increased CNS sensitivity to barbiturates and opiates, because uremia itself causes somnolence, malaise, etc.
   - dysfunction of thrombocytes; impairment of coagulation will lead to increased sensitivity to anticoagulants and antiplatelets
   - decreased tissue sensitivity to insulin, and also peripheral neuropathy
4. less responsive to drugs acting directly to the kidney, e.g. diuretics, uricosuric
5. more sensitive to nephrotoxic effects of analgesics, aminoglycosides, cephaloridin, cephalothin, amphotericin B, lithium, sulfonamides, tetracyclines, etc.
6. hypermagnesemia, in case the patient consumes high dose of Mg-containing antacids, causing somnolence, coma, cardiac arrhythmias, or death.

**Other Pharmacologic Problems in Renal Failure**

1. Urinary tract infections  
These require adequate antibiotic concentration in renal parenchyma and urine. Aminoglycosides enter urine only by glomerular filtration, hence they are not effective. Conversely, penicillins, cephalosporins, sulfonamides and trimethoprim enter urine by tubular secretion, therefore they are effective. Normal doses of these antibiotics are required to produce adequate urine levels.

2. Renal cyst infection  
It requires antibiotics that can penetrate cyst walls. Cotrimoxazole, chloramphenicol, fluoroquinolones can penetrate cyst walls, therefore they are effective. Penicillins, cephalosporins, aminoglycosides have poor penetration, hence they are not effective.

3. Neuromuscular blockers  
These accumulate in renal failure, producing increased and prolonged effect, and are worsened by accumulation of aminoglycosides, which also causes neuromuscular block, resulting in respiratory depression.

4. Creatinine is a base  
Therefore it is also actively secreted by renal tubule. Basic drugs (e.g. trimethoprim) will compete with it for tubular secretion, producing decreased creatinine clearance and increased creatinine serum.

5. Metabolic loads  
Acid load, e.g. by aspirin, NSAIDs; Alkali load, e.g. by antacids; Creatinine load, by anabolic and androgenic steroids; Mg load, by antacids, laxatives; K load, by K-penicillin, K-sparing diuretics, ACE inhibitors; Na load, by ampicillin, piperacillin, ticarcillin; Ureum load, by glucocorticoids, tetracyclines (antianabolic), hyperalimentation, protein; H₂O load, by NSAIDs, carbamazepine.

**Drug Use in Renal Failure**

1. NSAIDs are nephrotoxic  
Inhibition of renal prostaglandin by NSAIDs causes renal vasocostriction, leading to acute renal failure. NSAIDs can also cause drug
hypersensitivity, resulting in interstitial nephritis. Long-term use of NSAIDs can cause renal papillary necrosis.

Avoid usage in high-risk patients, i.e. elderly or compromised renal blood flow and volume depletion with concomitant urinary tract infection. If use is necessary, especially for long-term use, close monitoring of ClCr and regular urinalysis are required.

2. Analgesics
Acetaminophen is a safe analgesic, but not always effective. Opiates are used for more severe pain, but retention of active metabolites causes prolonged analgesia and respiratory depression.

Analgesic nephropathy can be avoided by using a single analgesic, not a mixture of more than 1 analgesic, especially in combination with caffeine or codeine.

3. Cardiovascular drugs
a. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Use in pre-existing renal disease due to atherosclerosis (compromised renal perfusion), and also pre-existing peripheral, cerebral, or coronary vascular diseases associated with renal dysfunction, which are usually reversible on drug withdrawal. Accumulation of these drugs in renal dysfunction requires dosage reduction. Renal function should be checked 3 to 4 days after starting therapy to ensure no decreased in GFR or increased in serum potassium.

b. Calcium channels blockers (CCBs)
These drugs are eliminated by hepatic metabolism, therefore are not much filtered via glomerulus, but secreted by organic anion pump in the renal tubule. In azotemia, organic acids compete for the active transport, therefore the dosage should be increased by doubling doses every 30 to 60 minutes until ceiling dose is reached or diuresis occurs. If this is ineffective, thiazide should be added. If it is still ineffective, loop diuretics should be given as continuous i.v. infusion.

b. Thiazides are generally not effective when ClCr is less than 25 mL/min.

c. Ototoxicity. Especially ethacrynicy acid, but also furosemide and bumetamide.

5. Antimicrobial agents (AMs)
Except aminoglycosides and vancomycin, most AMs have a wide therapeutic index, hence little or no dosage adjustment is normally made until the GFR is less than 20 mL/min.

AMs that are removed by dialysis should be administered after dialysis or a supplemental dose should be given after dialysis.

a. Aminoglycosides (AGs)
The bacteraemic efficacy correlates with therapeutic peak concentrations, while toxicity corresponds to rising trough levels. Therefore, the dosage adjustment should follow especially the interval approach. Peak and trough serum levels as well as ClCr should be measured to monitor therapy and avoid toxicity.

AGs aggravate pre-existing renal impairment, but also cause de novo acute renal failure. Nephrotoxicity is usually reversible, but ototoxicity may cause irreversible vestibular damage. Concomitant use of loop diuretics, especially ethacrynicy acid, greatly increases the risk of ototoxicity.

b. Vancomycin
This drug is nephrotoxic and ototoxic; therefore its plasma concentrations should be monitored. It is not dialyzed, hence after a single i.v. infusion, therapeutic levels can be maintained for 5 days in patients with end-stage RF on dialysis.

c. Tetracyclines
These drugs greatly increase BUN in RF due to its antianabolic effects and worsen the renal dysfunction. Therefore use of these drugs should be avoided in RF, except doxycycline and minocycline.

d. Antituberculosis drugs
Isoniazid, rifampicin and pyrazinamide are given in normal doses in RF. With isoniazid, pyridoxine should be added to prevent peripheral neuropathy.

Streptomycin and ethambutol should be avoided where possible. The major toxicity of streptomycin is vestibular, therefore if required, a reduced dose should be given 2 or 3 times weekly for the first 2 months, and the plasma levels must be monitored.

Ethambutol causes optic neuritis if excessive dosages are used or renal function is impaired. Therefore the dose should be reduced and given intermittently. If any visual changes develop, the drug should be discontinued immediately and medical advice must be sought.

e. Amphotericin B
This drug is nephrotoxic. The drug is used in renal failure only if there is no alternative, and plasma levels and renal function must be monitored closely. Since binding to lipoproteins decreases in RF, low plasma levels should be interpreted accordingly.

f. Antiviral drugs
Acyclovir and ganciclovir are eliminated by kidney; therefore the dose should be reduced in RF, because accumulation leads to CNS toxicity and unconsciousness.

6. Antianxiety drugs, Hypnotics and Antipsychotics
Patients with advanced RF are particularly sensitive to CNS depressant effects of these drugs, therefore therapy should be started with a smaller than normal dose.

7. Lithium and Antidepressants
Lithium should be avoided if possible or decrease the dose with careful monitoring of plasma levels. Tricyclic antidepressants and newer antidepressants can be prescribed in normal dosages.

8. Insulin
In reduced renal function, insulin requirement is also reduced; because it is eliminated by the kidney. In uremia, these is insulin resistance due to a post-receptor defect; this is corrected by dialysis. The compensatory response to hypoglycemia may also be impaired in uremia.
9. Oral antidiabetics (OADs)
Since chlorpropamide has an extended half-life of > 36 hours, its use in RF should be avoided. Glibenclamide also causes prolonged hypoglycemia in RF due to accumulation of an active metabolite which binds tightly to pancreatic β-cells.

Metformin is contraindicated in RF because the risk of lactic acidosis.

Glipizide is the OAD of choice in RF because of its short duration of action and its elimination by hepatic metabolism to inactive metabolites.

10. Gastrointestinal drugs
a. Antiulcers
Ranitidine is eliminated by liver and kidney, hence the dose should be reduced in severe RF. Proton pump inhibitors require no dosage adjustment in RF.

b. Antacids
Antacids containing Mg and Al (including sucralfate) should be avoided in severe RF or dialysis patients because of increased risk of toxicity.

11. Antigout drugs
Allopurinol is metabolized to oxypurinol. Its accumulation in renal failure causes rashes (in severe case, it can cause potentially fatal toxic epidermolysis), bone marrow depression and GI upset; therefore the daily dose should be reduced in RF.

Colchicine in excessive doses causes diarrhea, GI hemorrhage, rashes and renal impairment, hence the dose should be reduced in RF.

NOTE
Calculation of drug dosage in RF is based on various assumptions, i.e. no change and no interindividual variation in drug absorption, distribution, and metabolism; no active/toxic metabolites; drug elimination independent of dose (linear pharmacokinetics); no change and no interindividual variation in pharmacological response; stable renal function; and renal clearance of drug is proportional to ClCr. Therefore dosage adjustment based on calculation is only for initial estimation. It should be followed by further adjustments based on the plasma drug level (if available), and the most important on patient’s clinical response.

REFERENCES