

ANTIBIOTIC DOSAGE ADJUSTMENTS IN PATIENTS WITH RENAL COMPROMISE

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Infections occur in up to 88% of patients with acute renal failure and in up to 60% of patients with chronic renal failure.¹ Therefore, it is quite likely that the renally compromised patient will be treated with antibiotics during their lifetime that could potentially cause adverse reactions. The renal system is the primary mechanism by which the body regulates fluid and electrolyte balance as well as drug metabolism and elimination. Decreases in renal function can severely affect the mode by which drugs are distributed throughout and excreted from the body. A large population of the podiatric surgeon's patients are diabetic with disease-related complications including infection and diabetic nephropathy. It is a pharmacologic challenge to decide the appropriate initial and maintenance dosage for antibiotic therapy in these patients. Antibiotic metabolites can accumulate to toxic levels if dosages are not adequately adjusted.

There are many physiologic factors that can be measured to aid in determining how well an antimicrobial agent will be eliminated from the body. These include creatinine clearance, glomerular filtration rate, serum creatinine, and blood urea nitrogen. It is important to remember that drug absorption, volume of distribution, degree of protein binding, and biotransformation rates will be altered in renal patients so laboratory testing and calculations are not sufficient methods for the determination of dosage administration alone. Although certainly not all-inclusive, this article will review pharmacokinetic methods used for renal function determination as well as the most common antimicrobial agents used by podiatric surgeons and their adjustments for patients with renal compromise.

PHARMACOKINETICS

The amount of an antibiotic that is available in the systemic circulation after administration is termed the bioavailability of the drug. In the uremic state, drug absorption through the gastrointestinal system may be altered due to increases in gastric pH, gastroparesis, vomiting, and intestinal edema decreasing the drug's bioavailability.² The volume of

distribution (V_d) is calculated by dividing the total amount of drug administered intravascularly by the drug concentration in the plasma following equilibration.³ Therefore $V_d = \text{dose given} / \text{plasma concentration}$. The volume of distribution of many antibiotics can be increased in renal failure due to decreased plasma protein binding that will lower plasma concentrations.³ Acidic drugs such as dicloxacillin will have a much decreased plasma binding in renal failure possibly due to displacement of the drug from protein binding sites by other compounds.⁴

The half-life ($T_{1/2}$) of a drug is defined as the time it takes for the concentration of a drug to decrease by 50%.⁵ The $T_{1/2}$ of a drug is calculated by the following equation: $T_{1/2} = 0.693 (V_d) / \text{plasma clearance}$. As stated above, with renal insufficiency the V_d can increase, therefore increasing the $T_{1/2}$ and prolonging the time the drug is active in the body in a somewhat unpredictable fashion.

Biotransformation is a primarily hepatic process by which parent antibiotics are converted to their more water soluble forms and consequently excreted by the kidneys, liver, and to a lesser degree insensible loss mechanisms.⁶ By altering drug form, biotransformation decreases the activity of the antibiotic and forms byproducts of metabolism. These metabolites, such as potassium from penicillin, and sodium from carbenicillin metabolism can build up in the blood.⁷ Renal failure decreases the inherent ability to excrete these drug metabolites and the accumulation that occurs can result in toxic or hypersensitivity reactions. It is important to be aware that certain drugs may be metabolized faster in patients with renal failure due to compensatory mechanisms of the liver.⁸

The calculation of creatinine clearance approximates the rate at which blood is being filtered at the glomerular level. The average rate of glomerular filtration (GFR) is 120 mL/min.⁹ The formula for creatinine clearance as defined as follows:

$$\text{CrCl} = (140 - \text{age}) \times (\text{body weight in kg}) / 72 \times (\text{serum creatinine})$$

The calculation for females is 0.85 multiplied by this value.⁹ Creatinine clearance is approximated to be equal to GFR and therefore the terms are used interchangeably. This calculation is only accurate when the renal function of the patient is stable and serum creatinine remains constant. The creatinine clearance is assumed to be <10 ml/minute if the patient is oliguric.² This is to be differentiated from serum creatinine which is a reflection of glomerular filtration as well as muscle mass. Serum creatinine can actually be low or normal in patients with severe renal insufficiency if the patient has a low muscle mass seen in the cachetic or elderly.²

DOSAGE OF ANTIBIOTICS IN RENAL FAILURE

The loading dose is given to rapidly establish serum levels of the antibiotic in the therapeutic range. In general, the loading dose is not decreased or decreased modestly by 10%-20% regardless of the presence of renal insufficiency if the clinical assessment of the patient does not suggest edema, ascites, or dehydration.⁷ After a loading dose, maintenance doses may need to be adjusted based on the level of renal dysfunction that is present. These dosage adjustments will depend on the intrinsic properties of the antibiotic itself as well as the physiologic state of the patient. If a loading dose is not given, then three to four (average 3.3) maintenance doses must be given before a therapeutic serum level is achieved.⁷

Cephalosporins

First generation cephalosporins are active against all gram-positive cocci with the exception of *Enterococcus faecalis*.¹⁰ The most common oral agent used by podiatric physicians is cephalexin (Keflex). The T 1/2 in patients with normal renal function is approximately 40 minutes, but in patients with severe renal disease it can be prolonged to 16 hours.^{2,9} Normal oral dosage for cephalexin is 250-500 mg every 6 hours but the dose interval may need to be increased to every 8 or 12 hours depending on the glomerular filtration rate.^{2,9} Cephalexin is a highly protein bound drug achieving low CSF concentrations in patients with adequate renal function. However, in the uremic state, the degree of protein bound drug decreases causing influx of free unbound drug into the central nervous system (CNS). This can cause neurotoxicity

with symptoms such as dysarthria, confusion, myoclonus, seizures, and coma.¹ Cephalexin has also been associated with ototoxicity in renal patients.¹

The most common IV first generation cephalosporin used by podiatric surgeons in the setting of surgical prophylaxis is ceftazidime (Ancef). The T 1/2 for ceftazidime is normally 1.5 hours but can be increased to 36-70 hours with renal insufficiency. Ancef which is normally dosed at 0.5 - 2.0 g Q 8 hours will have an increased dosing interval of Q12 - Q 24-48 hours dependent on GFR.^{2,9} Ceftazidime is also associated with CNS neurotoxicity symptoms that can be slow to resolve even after discontinuation of drug therapy.¹

Second generation through fourth generation cephalosporins have increased activity against gram-negative bacteria with decreasing activity against gram-positive microorganisms.¹⁰ Third generation cephalosporins such as ceftriaxone and ceftazidime have long and short half-lives respectively and require dosing adjustments summarized in Table 1.

Carbapenems

Imipenem-Cilistatin is a broad-spectrum and potent antibiotic effective against gram-positive (with the exception of MRSA), gram-negative, and anaerobic organisms. Imipenem is rapidly broken down by renal tubular cells by the enzyme dehydropeptidase so it is administered with cilistatin, a dehydropeptidase inhibitor, which decreases drug uptake and therefore nephrotoxicity. The T 1/2 of imipenem is normally less than 1 hour but increases to 4 hours in renal disease states. This is of importance as high serum imipenem levels can induce seizures.¹ Dosage may need to be decreased to 25%-50% of normal dependent upon GFR.⁹

Fluoroquinolones

The fluoroquinolones have good oral bioavailability and are active against the majority of gram-negative rods including *Pseudomonas aeruginosa*.¹⁰ Ciprofloxacin (Cipro) is a 4-quinolone antibiotic with broad-spectrum activity against many gram-positive and gram-negative organisms used commonly for the treatment of osteomyelitis.¹¹ The T 1/2 of ciprofloxacin increases from 3-6 hours to 6-9 hours with renal disease.⁹ Dosage may need to be decreased to 75-50% of normal depending on GFR but there are minimal toxicities associated with this group.^{2,9}

Table 1

DRUG DOSAGE ADJUSTMENTS FOR PATIENTS IN RENAL FAILURE.

Drug	T ^{1/2} Normal/renal disease (Hours)	Dose for Normal Renal Function	GFR>50	GFR 10-50	GFR<10
Cephalexin	0.7/1.6	250-500 mg Q6 hr	Q8hr	Q12hr	Q12hr
Cefazolin	2 / 40-70	0.5 -2.0 g Q 8 hr	Q8hr	Q12hr	Q24-48hr
Cefotetan	3.5 / 13-25	1 -2 g Q 12 hr	100%	50%	25%
Ceftazidime	1.2 / 13-25	1 ? 2 g Q 8hr	Q8-12hr	Q24-48hr	Q48hr
Ceftriaxone	7-9 / 12-24	1- 2 g Q12-24 hr	100%	100%	100%
Clindamycin	2-4 / 3-5	150-900 mg Q6-8hr	100%	100%	100%
Ciprofloxacin	3-6 / 6-9	400mg IV or 500-750mg po Q12hr	100%	75%	50%
Vancomycin	6-8 / 200-250	1 g Q12 hr	500mg Q6-12hr	500mg Q 24-48hr	500 mg Q 48-96hr
Metronidazole	6-14 / 7-21	7.5mg/kg Q6-12hr	100%	100%	75%
Sulfamethoxazole	10 / 20-50	1g Q 8hr	Q 12hr	Q 18hr	Q 24hr
Trimethoprim	9-13 / 20-49	100-200mg Q12hr	Q12hr	Q18hr	Q 24hr

Vancomycin

Vancomycin is a tricyclic glycopeptide that is bactericidal against most gram-positive organisms and bacteriostatic against enterococci.¹⁰ Vancomycin is the drug of choice for methicillin resistant *Staphylococcus aureus* (MRSA). Vancomycin is most commonly dosed at 1 gram every 12 hours infused slowly over an hour for normal renal function.⁵ The half life of the drug is 0.5-1.5 hours and it is recommended to draw peak and trough levels to avoid toxicity. Trough concentrations are measured to ensure that serum vanco concentrations stay above the recommended level to maintain efficacy.² It is recommended to maintain a trough level of 5-10 ug/mL and a peak level of 20-40 ug.⁵ Trough levels should be drawn 1 hour before and peak levels one hour after administration respectively. In the case of renal failure, dosage can be adjusted to 500mg every 12-96 hours depending on GFR.⁹ Random vancomycin blood levels can also be drawn and the drug can be administered when the level falls to 7 -10 ug.¹² Some research suggests that the concomitant administration of vancomycin with aminoglycosides can result in nephrotoxicity so this should be avoided if possible.^{1,7}

Clindamycin

Clindamycin is a 7-chloro derivative of lincomycin with good activity against *Staphylococcus aureus* and most anaerobes including *Bacteroides fragilis*.¹⁰ As clindamycin is predominantly metabolized by the liver, its half life is not prolonged in renal disease and dosage adjustment is not usually necessary. Clindamycin administration is associated with the development of pseudomembranous colitis due to *Clostridium difficile*.^{3,9}

Metronidazole

Metronidazole (Flagyl) has good bactericidal activity against anaerobic bacteria and is popular for the treatment of anaerobic infections such as *Bacteroides* and *Clostridium*.¹⁰ Metronidazole has a T^{1/2} of 6-10 hours and is not cleared from the body by the kidney to a great degree. It may be necessary to reduce the dose to 75% of normal in patients with ESRD but otherwise the normal dose may be given.⁹ There have been isolated associations with metronidazole and peripheral neuropathy and vestibular toxicity.²

Sulfamethoxazole-Trimethoprim

Sulfamethoxazole-trimethoprim (SMX/TMP) is a combination of 160mg of trimethoprim and 800mg of sulfamethoxazole which block the biosynthesis of folate by microorganisms.¹⁰ SMX/TMP is used by podiatric physicians to treat susceptible gram-negative bacilli in osteomyelitis. Adverse reactions such as blood dyscrasias, nausea / vomiting, rash, and Stevens-Johnson syndrome associated with this drug are commonly attributed to the sulfa component.⁵ Normal dosing of the drug is one tablet every 12 hours. The T 1/2 of SMZ is 8-10 hours and 10-12 hours for TMP. The T 1/2 can be doubled in renal disease so the dosage may need to be reduced to 25% of normal every 12 hours.⁹

CONCLUSION

The patient with renal compromise presents a unique set of challenges to the podiatric physician in selecting the proper regimen of antibiotics. These challenges can be met and overcome with a solid understanding of physiology as well as taking the time to calculate and comprehend what the individual needs of the patient are. Knowledge of the properties of antimicrobials and the potential complications associated with them is also required. It may be necessary to consult a trusted pharmacist or nephrologist to arrive at an effective team approach for adequate and safe antibiotic therapy.

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