**Pharmacy Practice: Lecture 9 Dr. Haider Raheem**

**Dosing of Drugs in Renal Failure** **II**

**Effect of Hemodialysis**

**Conventional Dialysis**

Gentamicin

G.G.’s renal function continues to deteriorate to the extent that she requires hemodialysis. What additional alterations in her gentamicin dosing regimen are necessary when she is having dialysis?

Gentamicin has a molecular weight of about 500 and a relatively low Vd (averaging 0.25 L/kg), and is about 10% bound to proteins, all favoring effective removal by conventional hemodialysis. For a given patient, the observed dialysis clearance of gentamicin using conventional methods also depends on factors such as the physical properties of the dialysis filter, the blood and dialysate flow rates, and the length of dialysis. Studies indicate that dialysis clearance of gentamicin averages 45 mL/minute compared with an average plasma clearance of 5 mL/minute in patients with end-stage renal disease (ESRD).

Therefore, G.G.’s gentamicin dose must be adjusted to compensate for the amount of drug that will be removed by dialysis. Because drug removal represents a combination of drug elimination by the body and dialysis, the following equation can be used:

Cltotal = Cldial + Cl

where Cltotal is the total clearance of the drug during dialysis, Cldial is the clearance by dialysis, and Cl is plasma clearance. If dialysis clearance is high relative to plasma clearance, drug removal will be enhanced by the dialysis procedure. The total clearance of gentamicin in a patient with severe renal dysfunction during dialysis is 50 mL/minute (45 mL/minute + 5 mL/minute) or 10 times the clearance while off dialysis. Plasma clearance and dialysis clearance are related to the elimination half-life by the following equation:

$$t1/2= \frac{(0.693)(Vd)}{Cldial+Cl}$$

Thus, assuming a constant Vd of 17.5 L (i.e., 0.25 L/kg × 70 kg), the elimination half-life on dialysis is approximately 4 hours compared with 40 hours off dialysis. In addition, the extent (fraction) of drug removal (FD) during a timed dialysis run can be predicted from the following equation:

FD = 1 – e − (Cl + Cldial) (t/Vd)

where t is the duration of dialysis. Therefore, the fraction of gentamicin removed (FD) during a 4-hour conventional dialysis procedure is approximately 50%. If specific data are not available for dialysis and plasma clearance, the following equation will predict fraction removed using the elimination half-life data alone obtained during dialysis:

FD = 1 − e−(0*.*693*/*t1*/*2on) (t)

The estimated value of 50% removal is consistent with literature values indicating that 50% to 70% of a dose of gentamicin is removed during a 4-hour dialysis procedure. A limitation of this equation, however, is that it does not consider the redistribution of drug from the tissues back into the plasma after the dialysis procedure.

It generally is difficult to calculate an appropriate maintenance dose for patients having hemodialysis that will maintain peak and trough concentrations similar to patients with normal renal function, in part because of the large variability found in aminoglycoside pharmacokinetic parameters. As a compromise in patients receiving hemodialysis, gentamicin doses are given to achieve a predialysis trough concentration of approximately 3 mg/L. This can generally be achieved with a loading dose of 2 mg/kg, followed by a maintenance dose of 1 mg/kg after each dialysis session.

Ceftazidime

Why does the dose of ceftazidime in G.G. have to be adjusted because of her hemodialysis when this drug has such a large therapeutic window?

Because only 21% of ceftazidime is protein bound and its Vd is 0.2 L/kg, it should be readily removed by hemodialysis. The mean dialysis clearance of ceftazidime is 55 mL/minute, with 55% of the drug removed during 4 hours of conventional hemodialysis. A supplemental dose of ceftazidime should be given to G.G. after each hemodialysis session to maintain a therapeutic concentration. Half of the daily ceftazidime dose should be administered after each dialysis session.

**Phenytoin**

Protein Binding

R.S., a 24-year-old man with ESRD from rapidly progressive glomerulonephritis, is treated by hemodialysis three times weekly. He has a 7-year history of generalized tonic-clonic seizures and has been treated with phenytoin. He presents to the ED after having had a seizure lasting about 5 minutes. His mother states that he ran out of phenytoin 4 weeks ago. Because his plasma phenytoin concentration on admission was less than 2.5 mg/L, R.S. is given an IV loading dose of phenytoin: 15 mg/kg in 30 minutes. Additional admission laboratory work includes the following:

SCr, 8.6 mg/dL

BUN, 110 mg/dL

Potassium, 5.4 mEq/L

Calcium, 9 mg/dL

Albumin, 2.9 g/dL

Eight hours after administration of phenytoin, his level is 5 mg/L. Is this level subtherapeutic?

R.S. has severe renal disease, which will affect the total (bound plus free) phenytoin concentration achieved and how this concentration is interpreted. Decreased plasma protein binding will result in lower measured total phenytoin concentrations, and the calculated apparent Vd may increase. In patients with normal renal function, approximately 90% of the measured phenytoin is bound to albumin, and 10% is free. The free fraction of phenytoin is increased to about 20% to 25%in patients with uremia.

Because the free fraction for phenytoin is increased in patients with uremia, lower plasma concentrations will produce therapeutic effects that will be equivalent to those produced by higher phenytoin concentrations in patients with normal renal function. Phenytoin is an acidic drug that is bound primarily to albumin. A number of mechanisms have been proposed that account for the decreased binding, including (a) decreased albumin concentration, (b) accumulation of uremic byproducts that displace acidic drugs from their binding sites, and (c) alteration in the conformation or structure of albumin in uremic patients, resulting in a reduced number of binding sites or decreased affinity for drugs. Other acidic drugs with altered protein binding in renal disease are listed in Table 9-1.

Figure 9-1 illustrates changes in phenytoin levels when uremic and nonuremic patients are given equivalent doses.

**Table 9-1: Plasma Protein Binding (%) of Acidic Drugs in Renal Failure.**

|  |  |  |
| --- | --- | --- |
| Drug  | Normal  | Renal Failure |
| Cefazolin  | 85  | 69 |
| Cefoxitin  | 73  | 25 |
| Clofibrate  | 97  | 91 |
| Diazoxide  | 94  | 84 |
| Furosemide  | 96  | 94 |
| Pentobarbital  | 66  | 59 |
| Phenytoin  | 88–93  | 74–84 |
| Salicylate  | 87–97  | 74–84 |
| Sulfamethoxazole  | 66  | 42 |
| Valproic acid  | 92  | 77 |
| Warfarin  | 99  | 98 |



**Figure 9-1: Plasma phenytoin concentrations in uremic (○) and nonuremic (●) patients after 250 mg of intravenous (IV) phenytoin.**

The following equation should be used to correct for R.S.’s altered binding owing to his renal dysfunction and hypoalbuminemia:

$$CpNormal Binding= \frac{Cp'}{\left(0.48\right)\left(1-α\right)\left(\frac{P^{'}}{PNL}\right)+ α}$$

where Cp$'$ is the measured plasma concentration reported by the laboratory, and CpNormal Binding is the corrected plasma concentration that would be seen if the patient had normal renal function and normal albumin. Alpha (*α*) is the normal free fraction (0.1), P$'$ is the patient’s serum albumin, and PNL is normal albumin (4.4 g/dL). The factor 0.48 was derived from patients on hemodialysis and represents the decreased affinity of phenytoin for albumin.

For R.S., a total plasma phenytoin concentration of 5 mg/L is comparable to 13 mg/L in a patient without renal failure. Because this falls within the phenytoin’s therapeutic range of 10 to 20 mg/L, his measured level is not subtherapeutic.

The factor 0.48 should be used only to estimate changes in protein binding for patients with ESRD receiving hemodialysis. Data for patients with moderate renal disease are limited, and it is unclear what changes exist in the binding of phenytoin to albumin. For patients with normal or moderate renal impairment, the following equation should be used only if the serum albumin is low; the factor 0.48 should be omitted:

$CpNormal Binding= \frac{Cp'}{\left(1-α\right)\left(\frac{P^{'}}{PNL}\right)+ α}$

**Effect of Renal Failure on Metabolized Drugs**

**Procainamide**

F.G.’s procainamide level is 9 mg/L (normal, 4–8 mg/L) and her *N-*acetylprocainamide (NAPA) level is 34 mg/L (normal, 10–20 mg/L). How is the disposition of procainamide affected in patients with renal disease?

The pharmacokinetics of procainamide in patients with renal insufficiency is complex. Of the parent drug, 50% to 70% is excreted unchanged in the urine, and it can accumulate in patients with renal disease because plasma clearance values are reduced by as much as 70%. Procainamide is also partially acetylated to NAPA, which has antiarrhythmic properties similar to procainamide and is primarily excreted by the kidneys.

Figure 9-2 summarizes the elimination of procainamide and NAPA. The half-life of NAPA is longer, especially in patients with renal impairment, increasing from 6 hours in control subjects to as long as 40 hours in patients with ESRD. Because significant cardiac toxicity has occurred in some patients with NAPA levels greater than 30 mg/L, plasma level monitoring of both NAPA and procainamide is recommended. When procainamide is used in patients with renal failure, appropriate dosage reduction of procainamide may be necessary. It also is important to realize that the time required to reach steady state for NAPA in patients with renal failure may be as long as 5 days. Therefore, plasma levels measured early in therapy must be interpreted carefully, because these concentrations may be considerably lower than those that will be achieved under steady-state conditions.



**Figure 9-2: Elimination of procainamide (PA) and *N-*acetylprocainamide (NAPA) in subjects with normal renal and liver function.**

**Dose Adjustments and Precautions in Decreased Kidney Function**

**Table 9-2: Dose Adjustments and Precautions in Decreased Kidney Function.**

|  |  |
| --- | --- |
| Drug Class  | Agents Requiring Dose Adjustment |
| Antibiotics  | Almost all antibiotics require dosage adjustment (exceptions: ceftriaxone, clindamycin, linezolid, metronidazole, macrolides, nafcillin). |
| Anticoagulants  | Anticoagulants Enoxaparin, fondaparinux, apixaban, rivaroxaban, edoxaban, dabigatran. |
| Cardiac medications  | Atenolol, ACEIs, digoxin, nadolol, sotalol; avoid potassium-sparing diuretics if CrCl < 30 mL/min/1.73 m2. |
| Lipid-lowering therapy  | Clofibrate, fenofibrate, statins (particularly rosuvastatin). |
| Narcotics  | Codeine, use caution with meperidine and morphine; other agents may also accumulate. |
| Antipsychotic and antiepileptic agents | Chloral hydrate, gabapentin, lacosamide, levetiracetam, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin. |
| Hypoglycemic agents | Acarbose, alogliptin, canagliflozin, chlorpropamide, dapagliflozin, exenatide, glyburide, glipizide, insulins, liraglutide, metformin, saxagliptin, sitagliptin. |
| Antiretrovirals | Individualize therapy: Monitor CD4+ counts, viral load, and adverse effects (agents requiring dose adjustment: lamivudine, adefovir, emtricitabine, didanosine, stavudine, tenofovir, and zidovudine). |