Pharmacotherapy Considerations in Hemodialysis-Required Patients with COVID-19

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Pharmacokinetic Considerations

- Uremic patients may exhibit pharmacokinetic changes in:

- bioavailability,
- volume of distribution (Vd),
- Clearance

Bioavailability

- The oral bioavailability of a drug in sever uremia, may be decreased as a result of disease-related changes in gastrointestinal motility and PH that are caused by nausea, vomiting, and diarrhea.

- Mesenteric blood flow, may also be altered.

Volume of Distribution

- The apparent Vd, depends largely on:

- Drug-protein binding in plasma or tissue
- Total body water

- Renal impairment may alter the distribution of the drug as a result of:

- Changes in fluid balance
- Drug-protein binding (The plasma protein-binding of weak acidic drugs in uremic patients is decreased, whereas the protein binding of weak basic drugs is less affected.), or
- Other factors that may cause changes in the apparent Vd.

Clearance

Total body clearance of drugs in uremic patients is also reduced by either a decreased in the:

- GFR and possibly,
- Active tobular secretion
- Reduced hepatic clearance

Measuring Clcr

Cockcroft-Gault equation

- Serum creatinine should be at steady state.
- The weight in the equation reflects the ideal body weight.
- Use the actual weight if it is less than IBW.
- Use IBW if the difference within 20% of the IBW.
- Adjusted body wt. = IBW + 40% of the excess.

$$Cl_{Cr} = \frac{[140 - \text{age (yr)}] \times \text{body weight (kg)}}{72\ (C_{Cr})}$$

LBW (males) = 50 kg + 2.3 kg for each inch over 5 ft

LBW (females) = 45.5 kg + 2.3 kg for each inch over 5 ft

Classification of renal function based on Estimated GFR (eGFR) or Creatinine Clearance (Clcr)

Stage	Description[b]	eGFR[c] (mL/min/1.73m²)	Cl_{cr}[a,d] (mL/min)
1	Normal GFR	≥90	≥90
2	Mild decrease in GFR	60–89	60–89
3	Moderate decrease in GFR	30–59	30–59
4	Severe decrease in GFR	15–29	15–29
5	End-stage renal disease (ESRD)	<15 Not on dialysis Requiring dialysis	<15 Not on dialysis Requiring dialysis

DOSE ADJUSTMENT FOR UREMIC PATIENTS: Loading dose

- The loading drug dose is based on the apparent volume of distribution of the patient.

- It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore, **the loading dose of the drug is the same in uremic patients as in subjects with normal renal function.**

DOSE ADJUSTMENT FOR UREMIC PATIENTS: Maintenance dose

- The maintenance dose is based on clearance of the drug in the patient.

- In the uremic patient, the rate of renal drug excretion has decreased, leading to a decrease in total body clearance.
- Most methods for dose adjustment assume nonrenal drug clearance to be unchanged.
- The fraction of normal renal function remaining in the uremic patient is estimated from Clcr.

- After the remaining total body clearance in the uremic patient is estimated, a dosage regimen may be developed by:

1. decreasing the maintenance dose,
2. increasing the dosage interval, or
3. changing both maintenance dose and dosage interval.

Hemodialysis

- In practice, hemodialysis is most often used for patients with end-stage renal failure.
- Dialysis may be required from once every 2 days to 3 times a week, with each treatment period lasting for 2–4 hours.
- Dosing of drugs in patients receiving hemodialysis is affected greatly by the frequency and type of dialysis machine used and by the physicochemical and pharmacokinetic properties of the drug.
- Factors that affect drug removal in hemodialysis are listed in next slide.

Factors affecting dialyzability of drugs

Physicochemical and Pharmacokinetic Properties of the Drug	
Water solubility	Insoluble or fat-soluble drugs are not dialyzed—eg, glutethimide, which is very water insoluble.
Protein binding	Tightly bound drugs are not dialyzed because dialysis is a passive process of diffusion–eg, propranolol is 94% bound.
Molecular weight	Only molecules with molecular weights of less than 500 are easily dialyzed—eg, vancomycin is poorly dialyzed and has a molecular weight of 1800.
Drugs with large volumes of distribution	Drugs widely distributed are dialyzed more slowly because the rate-limiting factor is the volume of blood entering the machine—eg, for digoxin, V_D = 250–300 L. Drugs concentrated in the tissues are usually difficult to remove by dialysis.
Characteristics of the Dialysis Machine	
Blood flow rate	Higher blood flows give higher clearance rates.
Dialysate	Composition of the dialysate and flow rate.
Dialysis membrane	Permeability characteristics and surface area.
Transmembrane pressure	Ultrafiltration increases with increase in transmembrane pressure.
Duration and frequency of dialysis	

Effect of dialysis on drug elimination

- During the inter-dialysis period, the patient's total body clearance is very low and the drug concentration declines slowly.
- When the patient is placed on dialysis, the drug clearance (sum of the total body clearance and the dialysis clearance) removes the drug more rapidly.

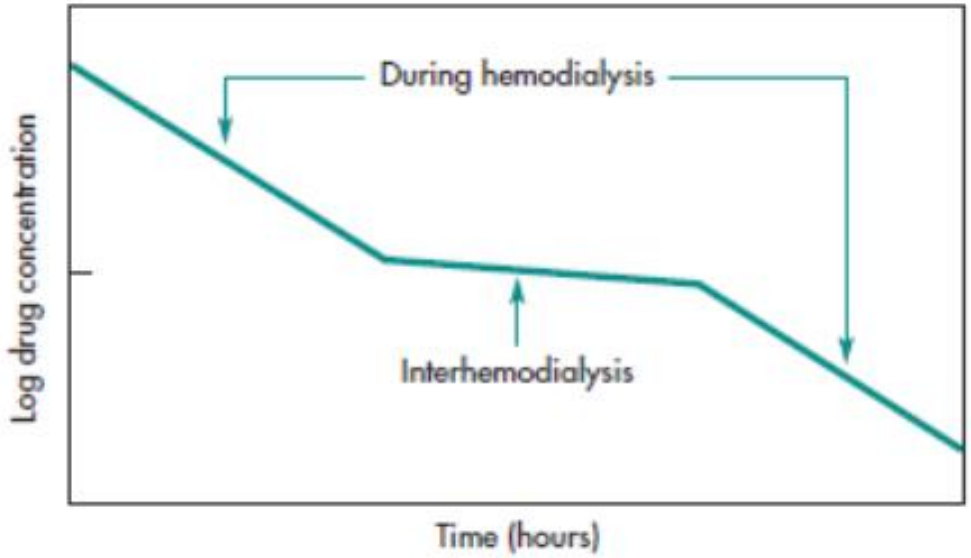

FIGURE 24-5 Effect of dialysis on drug elimination.

Proposed Medications for COVID-19

Investigational Therapeutics	Immune-based Therapeutics	Adjutants
Cap Favipiravir	Amp Tocilizumab	Amp Heparin
Cap Umifenovir (Arbidol)	Amp Anakinra	Amp Enoxaparin
Amp Remdesivir	Vial Convalescent Plasma	Tab Rivaroxaban
Tab Hydroxychloroquine	Vial IVIg	Tab Apixaban
Tab Chloroquine		Tab Naproxen
Tab Lopinavir-Ritonavir (Kaletra)		Tab Indomethacin
Tab Darunavir/Ritonavir		Amp NAC
Tab Sofosbuvir/Daclatasvir (Sovodak)		Tab Melatonin
		Cap Azithromycin

Proposed Medications

Investigational Therapeutics	Rout of Elimination
Cap Favipiravir	Metabolites are predominantly renally cleared.
Cap Umifenovir (Arbidol)	The major route of elimination is via the feces.
Amp Remdesivir	Excretion: Urine (74% [majority as metabolites]); feces (18%).
Tab Hydroxychloroquine	Excretion: Urine (15% to 25% [Tett 1993]; as metabolites and unchanged drug [up to 60%, McChesney 1966]); may be enhanced by urinary acidification.
Tab Chloroquine	Excretion: Urine (~70%; ~35% as unchanged drug); acidification of urine increases elimination; small amounts of drug may be present in urine months following discontinuation of therapy.
Tab Lopinavir-Ritonavir (Kaletra)	Excretion: Feces (83%, 20% as unchanged drug); urine (10%; <3% as unchanged drug)
Tab Darunavir/Ritonavir	Darunavir:Excretion: Feces (~80%, 41% as unchanged drug); urine (~14%, 8% as unchanged drug) Excretion: Urine (~11%, ~4% as unchanged drug); feces (~86%, ~34% as unchanged drug)
Tab Sofosbuvir/Daclatasvir (Sovodak)	Sofosbovir:Excretion: Urine (80%; primarily as metabolite); feces (14%) Daclatasvir: Excretion: Feces (88%, 53% unchanged); urine (6.6%, primarily unchanged)

Adjutants Therapeutics	Rout of Elimination
Amp Heparin	Urine (small amounts as unchanged drug); **Note:** At therapeutic doses, elimination occurs rapidly via nonrenal mechanisms. With very high doses, renal elimination may play more of a role;
Amp Enoxaparin	Excretion: Urine (40% of dose as active and inactive fragments; 10% as active fragments; 8% to 20% of antifactor Xa activity is recovered within 24 hours)
Tab Rivaroxaban	Excretion: Urine (66% primarily via active tubular secretion [~36% as unchanged drug; 30% as inactive metabolites]); feces (28% [7% as unchanged drug; 21% as inactive metabolites]).
Tab Apixaban	Excretion: Urine (~27% as parent drug); feces (biliary and direct intestinal excretion)
Tab Naproxen	Urine (95%; primarily as metabolites); feces (≤3%)
Tab Indomethacin	Urine (95%; primarily as metabolites); feces (≤3%)
Amp NAC	Excretion: Urine (13% to 38%)
Amp Methylprednisolone	Excretion: Urine (1.3% [oral], 9.2% [IV succinate] as unchanged drug)
Cap Azithromycin	Excretion: Oral, IV: Biliary (major route 50%, unchanged); urine (6% to 14% unchanged)

Dose Adjustments

Investigational Therapeutics

Drug	Dose adjustment in Hemodialysis
Cap Favipiravir	No data is available.
Cap Umifenovir (Arbidol)	About 40% is excreted in unchanged form, mostly through bile (38.9%) and an insignificant amount through the kidneys (0.12%). Therefore, it seems no dose adjustment is required.
Amp Remdesivir	**Do not be administered in ClCr<30 mi/min.**
Tab Hydroxychloroquine	Some experts recommend **a dose reduction of 50%** for GFR<10ml/min and hemodialysis.
Tab Chloroquine	Some experts recommend **a dose reduction of 50%** for GFR<10ml/min and hemodialysis.

Investigational Therapeutics-continued

Drug	Dose adjustment in Hemodialysis
Tab Lopinavir-Ritonavir (Kaletra)	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, a decrease in clearance is not expected.
Tab Darunavir/Ritonavir	There are no dosage adjustments provided in the manufacturer's labeling; however, the need for dosage adjustment is unlikely as renal clearance of darunavir is limited.
Tab Sofosbuvir/Daclatasvir (Sovodak)	There are no dosage adjustments provided

Immune-based Therapeutics

Drug	Dose adjustment in Hemodialysis
Amp MethylPrednisolon	There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Amp Tocilizumab (Actemra)	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, based on tocilizumab's molecular weight (148 kDa), it is unlikely to be significantly renally eliminated (expert opinion).
Amp Anakinra	-In ClCr<30 ml/min, Consider administering the prescribed dose every other day. -Not dialyzable (<2.5%)
Convalescent Plasma	Data not available.
Vial IVIg	Data not available, maybe it seems better not to administered.

Concomitant Medications- Anticoagulants

Drug	Dose adjustment in Hemodialysis
Amp Heparin	Not dialyzable. By PTT monitoring could be administered.
Amp Enoxaparin	Not dialyzable; Avoid use if possible.
Tab Rivaroxaban	Not dialyzable. Avoid use.
Tab Apixaban	According to the manufacturer, no dosage adjustment necessary. (PO: 10 mg twice daily for 7 days followed by 5 mg twice daily.)

Concomitant Medications-Antibiotics

Drug	Dose adjustment in Hemodialysis
Vancomycin	ESRD on intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): -Following **loading dose of 15 to 25 mg/kg**, give either **500 to 1,000 mg or 5 to 10 mg/kg after each dialysis session.** -Redosing based on pre-HD concentrations: <10 mg/L: Administer 1,000 mg after HD 10 to 25 mg/L: Administer 500 to 750 mg after HD >25 mg/L: Hold vancomycin -Redosing based on post-HD concentrations: <10 to 15 mg/L: Administer 500 to 1,000 mg
Linezolid	*Manufacturer's labeling:* Dialyzable (~30% removed during 3-hour dialysis session): No dosage adjustment necessary; administer after hemodialysis on dialysis days. The two primary metabolites accumulate in patients with renal impairment but the clinical significance is unknown; use with caution.

Concomitant Medications-Antibiotics- continued

Drug	Dose adjustment in Hemodialysis
Levofloxacin	Hemodialysis, intermittent (thrice weekly)[c]: Dialyzable (21% [4-hour dialysis session utilizing high-flux dialyzers]) 750 mg initial dose, then **either** 500 mg every 48 hours (manufacturer's labeling) **or** 250 mg every 24 hours (if daily dosing improves adherence [expert opinion])
Ciprofloxacin	Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Minimally dialyzable (<10%): IV: 200 to 400 mg every 24 hours **Note:** Dosing dependent on the assumption of 3 times weekly, complete IHD sessions.

Concomitant Medications-Antibiotics- continued

Drug	Dose adjustment in Hemodialysis
Amikacin	Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Dialyzable (20%; variable; dependent on filter, duration, and type of HD): **5 to 7.5 mg/kg every 48 to 72 hours**. -***Follow levels.*** -Re-dose when pre-HD concentration <10 mg/L; -Re-dose when post-HD concentration <6 to 8 mg/L. **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions.

Concomitant Medications-Antibiotics- continued

Drug	Dose adjustment in Hemodialysis
Azithromycin	No dosage adjustment or supplemental dose necessary.
Meropenem	Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): Meropenem and its metabolite are readily dialyzable: 500 mg every 24 hours. **Note:** Dosing dependent on the assumption of 3-times-weekly, complete IHD sessions.
Imipenem	End-stage renal disease (ESRD) on intermittent hemodialysis (IHD): -Use the dosing recommendation (for US labeling) for patients with a CrCl ≥15 to <30 mL/minute; -Administer dose after dialysis session and at intervals timed from the end of that dialysis session **or** 250 to 500 mg every 12 hours. **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions.

Concomitant Medications-Antibiotics- continued

Drug	Dose adjustment in Hemodialysis
Colistin	**Intermittent hemodialysis** (administer after hemodialysis on dialysis days): IV: Loading dose: **300 mg CBA (=9 mUint Colistimethate Sodium) followed by 130 mg CBA (=4mUnitColistimethate Sodium) once daily.** On dialysis days, a supplemental dose of 40-50 mg CBA (=1.5 mUnit Colistimethate Sodium) for a 3-4-hour intermittent hemodialysis (IHD) session, respectively, should be added to the daily maintenance dose. The dialysis session should occur toward the end of the dosing interval, and the supplement to the baseline (non-hemodialysis) daily dose should be administered with the next regular dose, after the dialysis session has **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions.

Concomitant Medications-Others

Drug	Dose adjustment in Hemodialysis
Tab Melatonin	There are no dosage adjustments provided.
Tab Naproxen	eGFR <30 mL/minute/1.73 m^2: Avoid use.
Tab Indomethacin	eGFR <30 mL/minute/1.73 m^2: Avoid use.
Amp NAC	There are no dosage adjustments provided in the manufacturer's labeling.
Amp Vitamin C	Use with caution.

Thanks for Attention