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Antibiotic Dosing in Sustained Low-Efficiency Dialysis in Critically Ill Patients

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Abstract

Purpose of review: Sustained low-efficiency dialysis (SLED) is increasingly used as a renal replacement modality in critically ill patients with acute kidney injury (AKI) and hemodynamic instability. There is, therefore, a greater need for the understanding of the antibiotic dosage and pharmacokinetics in these patients, to provide them with optimal therapy.

Sources of information: PubMed/Medline, Embase, and Google Scholar.

Methods: PubMed/Medline, Embase, and Google Scholar databases were searched using a combination of key words: dialysis, end stage renal disease, renal failure, sustained low efficiency dialysis, extended daily dialysis, prolonged intermittent renal replacement therapy (PIRRT), and antibiotic dosing. Studies that investigated antibiotic dosing and pharmacokinetics during SLED/extended daily dialysis/PIRRT were selected for this review.

Key findings: Eleven studies met inclusion criteria and selected for data extraction. The data with regard to dialysis specifications, type of antibiotic including dosages, drug clearances, and dosage recommendations are summarized in Table 1. It is a challenge to find therapeutic doses for antibiotics during SLED therapy because, in general, only aminoglycosides and vancomycin can be assayed in clinical laboratories.

Limitations: Although current studies on antibiotic dosing in SLED are limited due to diverse and undersized patient populations, antibiotic dosage adjustments for patients receiving SLED discussed here will serve as a valuable guide. Future large-scale research should focus on establishing guidelines for antibiotic dosage in SLED.

Implications: Pharmacokinetic principles should be taken into consideration for the appropriate dosing of drugs during SLED, yet it is vital to monitor response to drug to make sure therapeutic goals are achieved. Antibiotic dosing and timing relative to the initiation of SLED may be important to maximize either the time above the minimum inhibitory concentration (MIC) (time-dependent) or the peak to MIC ratio (concentration-dependent), balancing efficacy and toxicity concerns. Critical care physicians should liaise with nephrologists to make decisions regarding appropriate antibiotic dosing in patients undergoing SLED.

Abrégé

Justification : On recourt de plus en plus à l'hémodialyse prolongée à faible efficacité (SLED — *sustained low-efficiency dialysis*) comme thérapie de remplacement rénal chez les patients gravement malades présentant une insuffisance rénale aiguë (IRA) et une instabilité hémodynamique. Dès lors, il devient impératif de se pencher sur la posologie des antibiotiques et leur pharmacocinétique chez ces patients de façon à leur offrir le meilleur traitement possible.

Sources : Les bases de données PubMed/Medline, Embase et Google Scholar.

Méthodologie : Nous avons épluché les bases de données PubMed/Medline, Embase et Google Scholar à l'aide d'une combinaison de mots-clés : *dialysis* (dialyse), *end stage renal disease* (insuffisance rénale terminale), *renal failure* (insuffisance rénale), *sustained low efficiency dialysis* (hémodialyse prolongée à faible efficacité), *extended daily dialysis* (dialyse quotidienne prolongée), *prolonged intermittent renal replacement therapy* ou *PIRRT* (thérapie de remplacement rénal intermittente prolongée) et *antibiotic dosing* (posologie des antibiotiques). Ont été retenues pour cette revue les études qui exploraient la posologie des antibiotiques et leur pharmacocinétique dans les contextes de la SLED, de la dialyse quotidienne prolongée et de la PIRRT.

Constats : Onze études répondaient à nos critères d'inclusion. Les données obtenues sur les caractéristiques de la dialyse, de même que sur le type d'antibiotique, sa posologie, sa clairance et les doses recommandées sont résumées dans le Tableau 1. L'établissement de la dose thérapeutique d'antibiotique durant la SLED pose un défi puisque, généralement, seuls les aminoglycosides et la vancomycine peuvent être dosés en laboratoire clinique.

Limites : Bien que la fiabilité d'études traitant de la posologie des antibiotiques utilisés durant la SLED soit limitée, en raison notamment d'échantillons de sujets faibles et hétérogènes, les ajustements posologiques pour les patients traités par SLED discutés ci-après constitueront des balises utiles. De futurs essais à plus grande échelle devraient se concentrer sur l'établissement de lignes directrices concernant les doses thérapeutiques d'antibiotiques à administrer pendant la SLED.
Conclusion : Les principes pharmacocinétiques devraient être pris en compte pour établir la posologie d'antibiotique appropriée pendant la SLED. Il demeure toutefois crucial de surveiller la réponse au médicament pour s'assurer que les objectifs thérapeutiques sont atteints. La posologie d'antibiotiques et le moment d'initiation de la SLED pourraient s'avérer importants pour maximiser soit le temps au-dessus de la concentration minimale inhibitrice (en fonction du temps), soit le rapport entre le pic et cette même concentration (en fonction de la concentration), de façon à établir un équilibre entre les préoccupations liées à l'efficacité et celles relatives à la toxicité. Les médecins des unités de soins intensifs et les néphrologues devraient coopérer pour prendre des décisions conjointes quant à la posologie d'antibiotique appropriée pour les patients traités par SLED.

Keywords
antibiotics, SLED, sustained low-efficiency dialysis, pharmacokinetics, extended daily dialysis

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What was known before

Sustained Low Efficiency Dialysis (SLED) is becoming a common dialytic modality in critically sick patients. It utilizes diffusive and/or convective solute clearances. In addition to toxin removal, there is also drug removal, putting a patient at risk of drug dosing errors.

What this adds

This review adds valuable data on general pharmacokinetics and dose adjustment recommendations for commonly used drugs in the intensive care unit for critically sick patients.

Introduction

Patients suffering from acute kidney injury (AKI) require dialysis which provides adequate volume control, solute removal, and adequate hemodynamic stability and effectively corrects acid-base imbalances and electrolyte disturbances.[1] Various methods of dialysis are predominantly guided by the availability of machines, hemodialysis unit requirements such as specific patient needs, resource needs of the unit, and staff proficiency. Sustained low-efficiency dialysis (SLED) is considered to be "a conceptual and technical hybrid" of continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD). There are several advantages of SLED: stable hemodynamics due to decreased ultrafiltration rate, negligible solute disequilibrium due to low-efficiency solute removal, dialysis dose can be maximized due to prolonged treatment duration, and allows patients to undergo supplementary investigations or treatments during interdialytic periods, and has better mobility.[2]

SLED allows for these parameters, although its use in critical care medicine still requires further exploration in terms of better outcomes as compared with other dialysis methods.[2,3] CRRT uses advanced, expensive machines, requires trained intensive care unit (ICU) staff, and is usually labor intensive. SLED can provide renal replacement therapy over an extended period, but intermittently, using standard hemodialysis machines. SLED has been envisaged to safeguard hemodynamic stability and improve biochemical clearance with the cost-effectiveness of standard hemodialysis. This makes it an advantageous method of dialysis in developing countries where efficiency must be integrated with a careful watch on resources. Normally, the rate of blood flow is $\leqslant$5 mL/kg/min and dialysate flow is $\leqslant$ twice the blood flow rate.[4] The hemodynamic advantage of CRRT over IHD has been credited to a slower ultrafiltration rate as the same ultrafiltration target is achieved over 24 hours instead of the conventional 3 to 4 hours. SLED also has a similar advantage but at a lower cost. Lengthening the dialysis session time beyond the standard 4 to 5 hours of IHD and

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altering the rates of blood flow and dialysate flow are fundamental for executing SLED. Any machine with the ability to lower rates of blood flow and dialysate flow while increasing the time of hemodialysis can be used for SLED. Although there are benefits to SLED such as cost, small molecule clearance, (usually) no anticoagulation, hemodynamic stability, reduced risk of infection due to absence of bag handling, increased patient mobility and access, its aid in hyperkalemia, overnight treatment, and it being less labor intensive, there are disadvantages such as the higher start-up costs, unfamiliarity, and hypophosphatemia.[3]

The other disadvantages of SLED are similar to IHD; small and large solute clearances being low compared with CRRT, which reduces intradialytic urea disequilibrium and maintains equivalence between single and double pool urea kinetic models.[2] Furthermore, CRRT increases larger solute clearance including inflammatory mediators.[5] These larger solutes have a molecular weight more than the cutoff for low-flux hemodialysis membranes and higher convective clearance with appropriate porous membranes is needed for their removal.[6] Due to this, mainly diffusive solute clearance during SLED may be a disadvantage.[2] To maximize the small and large solutes removal during SLED, it is necessary to increase blood and dialysate flow rates to optimize diffusive clearance (for small solutes) and consider on-line haemodiafiltration with adequate porous membranes for higher convective clearance (for larger solutes).[2]

It is essential that clinicians understand the pharmacokinetic and pharmacodynamic properties, which influence drug dosing in SLED to make informed decisions on optimum patient treatment and ongoing management. In this article, we will be discussing the general pharmacokinetics of drugs during SLED, the pharmacokinetics of commonly used antibiotics in critically ill renal failure patients, and the various dosage adjustments which need to be made for these antibiotics during SLED. We believe that our article will be able to shed more light on the issues of antibiotic dosaging during SLED and how to overcome them.

Method

We searched PubMed/Medline, Embase, and Google Scholar using a comprehensive search strategy. The search strategy was designed using a combination of controlled vocabulary (eg, dialysis, ESRD, or end stage renal disease, renal failure) and key words (eg, sustained low efficiency dialysis or SLED, extended daily dialysis, prolonged intermittent renal replacement therapy or PIRRT, antibiotic dosing). There were no language or date restrictions on the searches. Additional literature was identified by hand searching the references of included articles and relevant reviews. Studies that investigated antibiotic dosing and pharmacokinetics during SLED/extended daily dialysis/prolonged intermittent renal replacement therapy (PIRRT) in comparison to other modalities of renal replacement therapy were included in this review. Studies that did not focus on SLED/PIRRT/extended daily dialysis were excluded. Studies focused solely on anticoagulation during SLED were also excluded. Two reviewers independently screened the list of identified abstracts using the predefined inclusion and exclusion criteria, and then extracted data from 11 selected studies for this review. The data with regard to dialysis specifications, type of antibiotic including dosages, drug clearances, and dosage recommendations were extracted into the Table 1.

Pharmacodynamic and Pharmacokinetic Considerations

Pharmacodynamic and pharmacokinetic factors should be considered when dosing antibiotics in critically ill patients receiving SLED. The pharmacodynamic profile of an antibiotic, whether its antimicrobial activity is concentration- or time-dependent, may influence the dosing regimen. Antibiotics such as aminoglycosides and quinolones are considered concentration-dependent antibiotics. For these drugs, a higher concentration relative to the minimum inhibitory concentration (MIC) of the organism results in greater antimicrobial efficacy. Conversely, β-lactams and vancomycin are considered time-dependent antibiotics meaning that the best determinant of antimicrobial efficacy is the percentage of time the drug concentration is above the MIC of the organism.[18] Timing of antibiotic administration relative to the initiation of SLED to maximize either the time above the MIC (time-dependent) or the peak to MIC ratio (concentration-dependent) is an important consideration and must balance efficacy and toxicity concerns.[19]

Changes in pharmacokinetic variables should also be considered when dosing antibiotics in critically ill patients receiving SLED. Absorption, distribution, and clearance of medications will be altered in this patient population. Oral absorption is unreliable in critically ill patients so medications are usually administered intravenously. Critically ill patients often receive large amounts of intravenous fluids which can influence drug distribution. Low concentrations of plasma proteins (primarily albumin) can result in a higher fraction of unbound drug in the plasma, which can alter drug distribution and elimination.[20] In addition, overall drug elimination can change daily as a patient's residual renal function improves or declines.

Clearance is the volume of reference fluid that is completely cleared of drug per unit time and is additive. The clearance of a renally eliminated drug in a patient undergoing renal replacement therapy will be determined by the patient's residual kidney function and the mode of renal replacement therapy. During the period on dialysis, drug clearance per hour is usually higher with SLED than CRRT and slower than during IHD.[21] However, because the duration of dialysis in SLED is usually 6 to 12 hours per day, the overall drug clearance per day is usually less than what is seen with CRRT but greater than what is seen with IHD.

Table 1. Studies of Antibiotic Dosage Analysis in SLED.

Study	Drug	Dose	No. of subjects	Dialysis machine	SLED characteristics	Pharmacokinetics in SLED	Recommendations
Ahern et al[7]	Vancomycin	Single dose 15 mg/kg IV	11	Fresenius 2008 H (Fresenius medical care)	Dialysate flow rate100 mL/min and blood flow rate 200 mL/min. Dialysis duration 24 h	Mean half-life 43.1 hr and mean clearance 24.3 mL/min. Mean volume of distribution 0.84 L/kg. Mean volume of distribution 0.84 ± 0.17 L/kg	Initial dose of 15 mg/Kg and measurement of serum drug levels at 24 h
Kielstein et al[8a]	Vancomycin	Single dose 1 g IV 12 h prior to dialysis	10	Batch dialysis system (GENIUS, Fresenius Medical care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Both dialysate and blood flow rate 160 mL/min. Dialysis duration 480 ± 6 min	Mean half-life 11.2 h. Mean clearance 2.1 L/h and 3.8 L/h based on analysis method. Mean volume of distribution 0.57 L/kg	Initial dose of 20-25 mg/kg and monitoring of drug levels for further dosing.
Manley et al[9]	Gentamicin*	Single dose of 0.6 mg/kg IV post dialysis	8	Fresenius Medical care, high-flux polysulfone F50 filter with surface are 0.5 m^2	Blood flow rate 200 mL/min and dialysate flow rate 300 mL/min. Duration of dialysis 480 min	Mean half-life 3.7 ± 0.8 h. Mean clearance 75.9 ± 38.4 mL/min/1.73 m^2. Mean volume of distribution 0.28 L/kg	2-2.5 mg/kg after hemodialysis to maintain optimal peak and trough levels at 7.5 µg/mL and 0.8 µg/mL, respectively
Kielstein et al[8a]	Meropenem	Single dose 1 g IV 6 h prior to dialysis	10	Batch dialysis system (GENIUS, Fresenius Medical care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Both dialysate and blood flow rate 160 mL/min. Dialysis duration 480 ± 6 min	Mean half-life 3.7 h. Mean clearances 2.3 and 5.1 L/h based on analysis method. Mean volume of distribution 0.72 L/kg	0.5-1 g every 8 h
Braune et al[10]	Meropenem	Varying doses of 0.5 g, 1 g and 2 g IV over 30 min every 8 h	19	GENIUS batch system (Fresenius Medical Care, Bad Homburg, Germany) with Fresenius FX 60 filter (surface area 1.4 m^2)	Mean SLED duration 315 min. Mean blood/dialysate flow rate 250 mL/min and ultrafiltration rate 500 mL/h.	The PTA for 40% fT $>_{MIC}$ and 100% fT $>_{MIC}$ was >95% with a meropenem dose of 0.5 g 8 hourly for *Pseudomonas aeruginosa* (MIC ⩽2) in patients without residual diuresis, whereas it was >95% and 93% with a dose of 1 g 12 hourly and 2 g 8 hourly, respectively, in patients with 300 mL/d residual diuresis. In patients with residual diuresis, FTA of 97% was achieved with a dose of 2 g 8 hourly for 100% fT $>_{MIC}$	Pharmacokinetic properties are significantly influenced by the degree of residual diuresis in patients undergoing SLED. Therapeutic drug monitoring may help optimize individual dosing
Burkhardt et al[11]	Ertapenem	Single dose of 1 g IV	6	Batch dialysis system (GENIUS, Fresenius Medical care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 160 mL/min. Dialysis duration 480 min	Half-life 6.7 h. Mean clearance 49.5 ± 10.9 mL/min. Volume of distribution 15.9 ± 3.2 L	1 g/d
Fiaccadori et al[12]	Linezolid	Single dose of 600 mg IV before dialysis	15	Fresenius Medical Care (low-flux polysulfone filters with 1.6 m^2 surface area)	Blood flow 200 mL/min and dialysate flow 100 mL/min. Dialysis duration 8-9 h	Half-life 5.88 h and clearance 33.3 mL/min. Volume of distribution 30.19 L	Drug should be administered toward the end of dialysis session
Czock et al[13b]	Moxifloxacin	Single dose of 400 mg IV 8 h prior to dialysis	10	GENIUS batch system (Fresenius Medical Care, Bad homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 161 ± 4 mL/min. Dialysis duration 481 ± 9 min	Mean half-life 6 h and mean clearances 2 L/h and 3.1 L/h based on analysis method. Mean volume of distribution 3.8 L/kg	Standard 400 mg/d irrespective of liver impairment

(continued)

Table 1. (continued)

Study	Drug	Dose	No. of subjects	Dialysis machine	SLED characteristics	Pharmacokinetics in SLED	Recommendations
Czock et al[13b]	Levofloxacin	Single dose of 250/500 mg IV 12 h prior to dialysis	5	GENIUS batch system (Fresenius Medical Care, Bad homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 161 ± 4 mL/min. Dialysis duration 481 ± 9 min	Mean half-life 10.3 h and mean clearances 2.93 L/h and 3.12 L/h based on analysis method. Mean volume of distribution 1.71 L/kg	Dosage adjustment is necessary and drug should be given after dialysis
Lorenzen et al[14]	Ampicillin/ sulbactam	Single dose of 2 g/1 g IV 3 h prior to dialysis					
Multiple doses of 2 g/1 g twice daily for 4 days	12	GENIUS batch system (Fresenius Medical Care, Bad homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 162 ± 6 mL/ min. Dialysis duration 442 ± 77 min	Mean volume of distribution for ampicillin/sulbactam were 13.1 ± 11.1 L and 22 ± 21.8 L, respectively, mean half-life 2.8 ± 0.8 h and 3.5 ± 1.5 h, respectively, mean clearances 80.1 ± 7.7 mL/min and 83.3 ± 12.1 mL/min, respectively			
No significant drug toxicity with twice daily dosing	Twice daily dosing 2 g/1 g with one dose given after dialysis						
Clajus et al[15]	Trimethoprim/ sulfamethoxazole	15 mg/kg/d and 95 mg/ kg/d IV	1	GENIUS batch system (Fresenius Medical Care, Bad homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 170 ± 41 mL/min. Dialysis duration 442 ± 101 min	Clearances 94 ± 20.2 mL/min and 51 ± 18.8 mL/min, respectively	Further studies needed to establish dosing recommendations
Strunk et al[16]	Colistin	6 million units loading dose and 3 million units every 8 h	1	High flux 1.3 m^2 dialyzer	Mean blood and dialysate flow rate 191 mL/ min and 121 mL/min, respectively. Average dialysis duration 552 min	Colistin clearance 54-71 mL/min and colistin methanesulfonate 25-62 mL/ min	Recommends loading dose of 6 million units and maintenance of 3 million units every 8 h
Konig et al[17]	Ceftazidime	1-2 g IV over 30 min 8-12 hourly	16	Genius batch system (Fresenius Medical Care, Bad Homburg, Germany) with Fresenius FX 60 filter (surface area 1.4 m^2)	Mean duration of SLED 299 min. Mean blood/ dialysate flow rate 264 mL/min and mean ultrafiltration 540 mL/h	Mean clearance on SLED was 5.32 L/h versus 1.06 L/h off SLED. PTA for 50% fT $>_{MIC}$ was 98% at a dose of 1g IV 8 hourly.	Ceftazidime at a dose of 1g IV 8 hourly and 2g IV 12 hourly is adequate for attaining 50% fT $>_{MIC}$ and 100% fT$>_{MIC}$, respectively, for susceptible pathogens (MIC ⩽8mg/L)

Note. SLED = sustained low-efficiency dialysis; kg = kilogram; IV = intravenous; PTA = probability of the target attainment; fT >MIC = blood levels of the given drug to be more than minimum inhibitory concentration for a specified duration of the dosing interval; FTA = fractional target attainment.

[a]Denotes single study but 2 different antibiotics.

[b]Denotes single study but 2 different antibiotics.

*Slow daily home dialysis

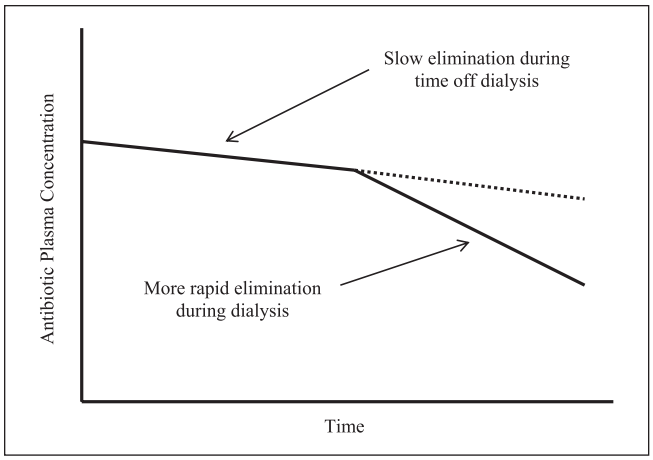

Figure 1. Theoretical drug elimination curve in a patient receiving SLED showing a slower elimination phase while off dialysis followed by a more rapid elimination phase on dialysis.

Because clearance is additive, total clearance (CL_T) during SLED may be conceptualized as follows[22]:

$$CL_T = CL_{pat} + CL_D,$$

where CL_{pat} = patient's intrinsic clearance (sum of the patient's residual renal and non-renal clearance); CL_D = clearance from dialysis. In some patients, CL_{pat} will be so low that practically CL_T is equivalent to CL_D.

Drug clearance from dialysis will be determined by the dialysis prescription and includes dialysate and blood flow rates as well as the type of dialyzer used. Drug clearance is also influenced by the mechanisms of solute removal, which in the case of SLED, are convection and diffusion. Transport of solutes across the hemofilter membrane via convection is the movement of plasma water from the vascular compartment to the effluent compartment, and the related bulk transport.[23] Rates of convection depend on the rate of ultrafiltration, which is guided by the transmembrane pressure gradient created by the blood and ultrafiltrate pumps in the system. Transmembrane concentration gradient of the solute or medication results in the diffusive transport of solutes across the hemofilter membrane. Diffusion is the most effective method for removal of small molecules (<1000 daltons).[23]

In patients receiving SLED, the overall elimination will be biphasic with a slower elimination rate while the patient is off dialysis and a faster elimination rate during dialysis. The initial slow clearance represents the patient's intrinsic clearance (CL_{pat}) and the secondary phase is a more rapid elimination consisting of CL_{pat} and CL_D (clearance during SLED) (Figure 1). The dialysate and blood flow rates as well as the duration of SLED and the dialysis filter will have an impact on drug clearance. Because SLED is delivered for an extended period (6-12 hours each day) and antibiotics are administered intermittently (as opposed to a continuous infusion), timing of drug administration relative to the start of SLED will influence overall drug exposure.[24] Any medications administered as a continuous infusion to a patient receiving SLED would need to have the infusion rate adjusted to different rates while on versus off dialysis. Therefore, it is important to consider the exact SLED prescription and timing of antibiotic administration when interpreting published pharmacokinetic studies for antibiotics in patients receiving SLED.

Careful dosing of antibiotics in patients receiving renal replacement therapy is important to prevent adverse events while ensuring therapeutic plasma concentrations. When evaluating the literature on antibiotic dosing during SLED, it is important to consider the dialysis procedure used including dialysate and blood flow rates, the type of dialyzer, and the duration and frequency of dialysis.[25]

Discussion on Individual Antibiotics

Although current studies on antibiotic dosing in SLED are limited due to diverse and undersized patient populations, antibiotic dosage adjustments for patients receiving SLED will be discussed here, and studies are summarized in Table 1. Table 2 describes normal pharmacokinetic properties of commonly used antibiotics.

Ampicillin and Sulbactam

The combination of ampicillin and sulbactam is a commonly used antibiotic for a myriad of infections, and better understanding of its pharmacokinetics in the setting of SLED is essential for correct therapeutic dosing. The primary route of clearance for both ampicillin and sulbactam is renal in normal subjects.[26] The volume of distribution for ampicillin and sulbactam is 0.22 L/kg and 0.30 L/kg, respectively, and plasma protein binding is moderate.[26,27] Half-lives of ampicillin and sulbactam in normal individuals are 1.4 and 1.7 hours, respectively, whereas in patients with stage 5 chronic kidney disease, it is 17 and 15 hours, respectively.[14] In a prospective open-label observational pharmacokinetic study, 12 critically ill adult patients with AKI on SLED were administered a single dose of ampicillin/sulbactam 2 g/1 g.[14] Dialysis was performed using a polysulfone high-flux dialyzer with mean blood and dialysate flow rates of 162 ±6 mL/min. Dialysis was started about 3 hours after the administration of the ampicillin/sulbactam and continued for an average duration of 442 ± 77 minutes. Three patients received multiple doses of ampicillin/sulbactam 2 g/1 g given twice daily for 4 days. Noncompartmental pharmacokinetic analysis revealed ampicillin/sulbactam volume of distribution to be 13.1 ± 11.1 L and 22 ± 21.8 L, respectively; dialysis clearances were 80.1 ± 7.7 mL/min and 83.3 ± 12.1 mL/min, respectively; and half-lives were 2.8 ± 0.8 hours and 3.5 ± 1.5 hours, respectively. In this study, the half-life of ampicillin/sulbactam was longer than the half-life observed in healthy subjects, shorter than in patients with chronic kidney disease

Table 2. Pharmacokinetic Properties of Antibiotics in Healthy Adults.

Drug	Renal clearance	Volume of distribution	Protein binding	Normal half-life	Half-life in renal failure
Ampicillin/Sulbactam[14, 26, 27]	144 ± 64 mL/min (ampicillin) 136 ± 58 mL/min (sulbactam)	0.22 L/kg (ampicillin) 0.30 L/kg (sulbactam)	28% (ampicillin) 38% (sulbactam)	1.4 h (ampicillin) 1.7 h (sulbactam)	17 h in stage 5 CKD (ampicillin) 15 h in stage 5 CKD (Sulbactam)
Vancomycin[31, 32]	80%-90% of a single dose excreted as unchanged drug in the urine within 24 h.	0.4-1 L/kg	10%-50%	6 h	>168 h in severe renal failure
Gentamicin[32, 33]	Almost entirely by filtration 80-90 mL/min/1.73 m^2	0.14-0.70 L/kg	Negligible	2-3 h	50-70 h
Meropenem[10, 32, 34]	70% of a single dose excreted as unchanged drug over 12 h. 139-252 mL/min	12.5-20.7 L/kg	2%	1 h	>5.7 h
Ertapenem[11, 32, 37]	40% of a single dose excreted as unchanged drug. 22.7 mL/min	0.11-0.12 L/kg	84%-96%	4 h	4.4 h in mild renal insufficiency to 14.1 h in ESRD
Linezolid[12, 32, 38, 39]	30%-35% excreted as unchanged drug in the urine at steady state. 50% excreted as the two major metabolites. 50 mL/min	40-50 L	31%	4.5-5.5 h	Not significantly altered by renal failure
Moxifloxacin[13, 40]	20% excreted as unchanged drug in the urine 2.45-2.67 L/h	2.45-3.55 L/kg	39%-52%	12 h	Not significantly altered by renal failure
Levofloxacin[32, 40]	60%-87% of a single dose excreted as unchanged drug in the urine within 72 h 91-140 mL/min	0.92-1.36 L/kg	24%-38%	6-8 h	>20 h
Trimethoprim/ Sulfamethoxazole[15, 41]	80% (trimethoprim) and 20% (sulfamethoxazole) recovered in the urine as unchanged drug	100-120 L (trimethoprim) 12-18 L (sulfamethoxazole)	44% (trimethoprim) 70% (sulfamethoxazole)	6-17 h (trimethoprim) 9 h (sulfamethoxazole)	Prolonged
Colistin and Colistimethate (CMS)[43, 44]	100 mL/min which is 2/3 of total clearance (CMS) 1.9 mL/min (colistin)	14.0L (CMS) 12.4L (colistin)	59%-74% (colistin)	2-3 h (CMS)	2-3 days in patients with anuria (CMS)
Ceftazidime[17, 28]	70%-90% excreted unchanged in the urine within 24 h	18 L/1.73 m^2	17%	1.5-2.5 h	15 h

Note. CKD = chronic kidney disease; ESRD = end-stage renal disease; CMS = colistimethate sodium.

stage 5.[14] For the 3 patients who received ampicillin/sulbactam 2 g/1 g twice daily for 4 days, there was no accumulation of drug to toxic levels. This study suggests that SLED clears ampicillin/sulbactam effectively and to a greater extent than regular IHD. The authors suggest that when SLED is started within 3 hours after administration of ampicillin/sulbactam, it should be given twice daily at a dose of 2 g/1 g with 1 dose given after dialysis.[14]

Ceftazidime

In normal subjects, the volume of distribution of ceftazidime is consistent with the extracellular space (18 L/1.73 m^2).[28] Most of the drug is eliminated as unchanged drug in the urine and plasma protein binding is low (17%).[28] The normal half-life of ceftazidime is about 1.5 to 2.5 hours and in patients with renal failure, it is about 15 hours.[17] Ceftazidime has time-dependent bactericidal effect that requires blood levels to be more than MIC for at least 50% of the dosing interval (50% fT $>_{MIC}$) and latest evidence indicates that critically ill subjects with severe infections to have a target of 100% fT$>_{MIC}$.[29,30] Konig et al conducted single-arm, prospective, observational pharmacokinetic study in 16 adult ICU patients undergoing SLED.[17] Ceftazidime 1 to 2 g was administered intravenously (IV) over 30 min every 8 to 12 hours at the physician's discretion. The mean duration of SLED was 299 min with mean blood/dialysate flow rate of 264 mL/min and mean ultrafiltration was 540 mL/h.[17] Two-compartment linear population pharmacokinetic models were used for analysis. The mean clearance of ceftazidime on SLED was 5.32 L/h versus 1.06 L/h off SLED.[17] It was found that the probability of the target attainment (PTA) for 50% fT $>_{MIC}$ was 98% for ceftazidime at a dose of 1g IV every 8 hours.[17] This study concluded that ceftazidime at a dose of 1 g IV 8 hourly and 2 g IV 12 hourly is adequate for attaining 50% fT $>_{MIC}$ and 100% fT$>_{MIC}$, respectively, for susceptible pathogens (MIC $\leq$8mg/L).[17]

Vancomycin

In normal subjects, the majority of intravenously administered vancomycin is recovered unchanged in the urine.[31] Mean half-life is 6 hours in normal subjects and >168 hours in severe renal failure patients.[32] Vancomycin penetration into tissues is variable with a volume of distribution 0.4 to 1 L/kg and plasma protein binding capacity of 10% to 50%.[31] Protein binding capacity is low in patients with severe renal failure (18%-20%).[32] Therapeutic serum vancomycin levels are affected by the SLED dialysate and blood flow rates. Studies have advocated initial dose of vancomycin to be 15 to 25 mg/kg depending on the dialyzer characteristics and monitoring of drug concentration to determine further dosing in patients on SLED.[7,8] A prospective trial involving critically ill patients receiving SLED for AKI studied pharmacokinetics of vancomycin. The mean blood flow rate and dialysate flow rate were 200 mL/min and 100 mL/min, respectively. Patients received single dose of vancomycin 15 mg/kg depending on actual body weight. Single-compartment model of pharmacokinetic analysis was used. The mean volume of distribution was 0.84 $\pm$ 0.17 L/kg with mean half-life of 43.1 hours and clearance of 24.3 mL/min; dosing intervals were 24 to 72 hours. This study recommends initial vancomycin dose of 15 mg/kg and measurement of serum drug levels at 24 hours to ascertain the need for additional doses, as there was wide variability in vancomycin half-life.[7] Another prospective study involving intensive care patients with anuric AKI where the SLED dialysate flow rate and blood flow rate was 160 mL/min, and single dose 1g of vancomycin administered 12 hours prior to dialysis showed that the mean volume of distribution was 0.57 L/kg, mean vancomycin half-life of 11.2 hours, and mean clearances of 2.1 L/h and 3.8 L/h based on analysis method used. In this study, noncompartmental methods with presumed steady-state conditions were used to study pharmacokinetics of the drug. The initial recommended dose of vancomycin was 20 to 25 mg/kg with drug concentration monitoring for further dosing.[8]

Gentamicin

Gentamicin provides a good coverage against gram-negative organisms, and maintenance of adequate peak and trough levels is crucial to retain effective coverage in patients on SLED. In normal subjects, gentamicin distribution is approximately equivalent to the extracellular space, although the volume of distribution may be much larger in some patients (0.14-0.70 L/kg).[33] The elimination of gentamicin is almost exclusively by glomerular filtration and plasma protein binding is negligible.[33] Half-life of gentamicin is 2 to 3 hours, while it is 50 to 70 hours in renal failure patients.[32] In a prospective, open-label pharmacokinetic slow daily home hemodialysis study involving ESRD, patients with SLED parameters of 200 mL/min blood flow and 300 mL/min of dialysate flow received single dose of gentamicin 0.6 mg/kg post dialysis depending on actual body weight.[9] The mean half-life of gentamicin was 3.7 $\pm$ 0.8 hours during dialysis and 20.4 $\pm$ 4.7 during interdialytic period. The mean drug clearances during interdialytic and intradialytic phases were 15.8 $\pm$ 4 mL/min/1.73 m^2 and 75.9 $\pm$ 38.4 mL/min/1.73 m^2, respectively. Mean volume of distribution was 0.28 L/kg that was comparable to values in healthy individuals. Gentamicin rebound was <4% and was attributed to smaller dialyzer size, slower rates of blood and dialysate flow. Due to this reduced drug rebound, which gives adequate time for redistribution, it was recommended that 2 to 2.5 mg/kg of gentamicin administration intravenously post dialysis to have optimal therapeutic levels and gram-negative coverage.[9]

Meropenem

The majority of meropenem is excreted unchanged in the urine in normal subjects, and distributes into multiple different tissues with a volume of distribution 12.5 to 20.7 L/kg

and protein binding is very low (2%).[34] Normal half-life of meropenem is 1 hour and is prolonged in renal failure patients to >5.7 hours.[10,32] Pharmacokinetics of meropenem has been studied in the setting of SLED, and its clearance has been shown to be almost same as in other forms of CRRT. Furthermore, meropenem has time-dependent bactericidal effect that requires blood levels to be more than MIC for at least 40% of the dosing interval (40% fT $>_{MIC}$) with latest evidence indicating to have a target of 100% fT$>_{MIC}$ in critically ill septic patients.[30,35] A prospective study involving critical care patients with anuric AKI were given single dose meropenem 1 g intravenously 6 hours prior to SLED where the SLED dialysate flow rate and blood flow rate was 160 mL/min.[25] Noncompartmental methods of pharmacokinetic calculations were done with presumed steady-state conditions. This study found that the mean half-life of meropenem in SLED (3.7 hours) was comparable to that of reported half-life for IHD (2.9 hours), but shorter than the reported half-life for CRRT (7.5 hours). The mean volume of distribution was 0.72 L/kg and mean clearances of meropenem by SLED were 2.3 and 5.1 L/h depending on the analysis method and were comparable to reported clearances for IHD (4.7-4.9 L/h) and CRRT (3.5 L/h). The recommended dose of meropenem according to this study was 0.5 to 1 g every 8 hours to maintain effective plasma levels.[8] A recent prospective observational study by Braune et al tested pharmacokinetic properties of meropenem in 19 septic patients undergoing SLED.[10] Two-compartment linear population pharmacokinetic model was used.[10] The mean SLED duration was 315 min with mean blood/dialysate flow rate of 250 mL/min and ultrafiltration rate of 500 mL/h. Varying doses of 0.5 g, 1 g and 2 g meropenem was administered IV over 30 min every 8 hours at the discretion of the physician.[10] The PTA for 40% fT $>_{MIC}$ and 100% fT $>_{MIC}$ was >95% with a meropenem dose of 0.5 g every 8 hours for *Pseudomonas aeruginosa* (MIC ⩽2) in subjects without residual diuresis, whereas it was >95% and 93% with a dose of 1 g every 12 hours and 2 g every 8 hours, respectively, in patients with 300 mL/d residual dieresis.[10] Furthermore, in these patients with residual diuresis, fractional target attainment (FTA) of 97% was achieved with a dose of 2 g every 8 hours for 100% fT $>_{MIC}$.[10] In a recent national survey of pharmacists on antibiotic dosing recommendations in SLED, it was found that there was 4 to 12 fold variation in antibiotic dosing recommendations across institutions, and most frequently recommended regimen for meropenem was 1 g every 12 hours.[36]

Ertapenem

Ertapenem is active against commonly encountered aerobic and anaerobic gram-positive and gram-negative organisms. The renal elimination of ertapenem involves glomerular filtration and tubular secretion as well as renal metabolism.[37] Half-life of ertapenem is 4 hours in health people, while it is 4.4 hours in mild renal insufficiency to 14.1 hours in ESRD[11,32] and is extensively protein bound (84%-96%) with a relatively small volume of distribution for total drug (0.11-0.12 L/kg).[37] Standard dose of ertapenem without any dose adjustments in the setting of SLED maintains therapeutic levels to provide effective coverage. In a prospective open-label study in critical care patients with AKI on SLED were given single dose of 1 g ertapenem.[11] Mean blood flow and dialysate flow rate was 160 mL/min. Noncompartmental method of pharmacokinetic analysis was done. Half-life of ertapenem was 6.7 hours, volume of distribution was 15.9 ± 3.2 L, and the clearance was 49.5 ± 10.9 mL/min that was similar to clearances observed in critical care patients without requiring dialysis and healthy volunteers. This shows that patients being treated with SLED should be given standard 1 g/d dose of ertapenem to have therapeutic levels that provide effective antibacterial coverage.[11]

Linezolid

In normal subjects, plasma protein binding of linezolid is low to moderate (31%) and the volume of distribution is roughly equal to total body water 40 to 50 L.[38] The half-life of linezolid is 4.5 to 5.5 hours, which is not markedly altered by renal failure, and elimination involves hepatic metabolism to inactive metabolites (50%), and renal clearance of intact linezolid is about 30% of a dose as unchanged drug in the urine at a steady state.[12,32,39] Linezolid pharmacokinetics in SLED has been studied, and it was suggested that the drug be administered at the end of dialysis session to maintain optimal therapeutic levels and MIC. In a prospective study involving critically sick oliguric AKI patients on SLED (blood and dialysate flow rate of 200mL/min and 100mL/min respectivey), a single dose of linezolid 600mg was administered prior to SLED initiation.[12] Single-compartment pharmacokinetic analysis revealed linezolid volume of distribution was 30.19 L, half-life of 5.88 hours with clearance rate of 33.3 mL/min, and in most cases drug levels were <4 mg/L that is lower than the MIC required to target staphylococcus species. To maintain MIC, it was recommended that linezolid administration be done at the end of dialysis session.[12]

Moxifloxacin and Levofloxacin

The major route of elimination of moxifloxacin in normal subjects is hepatic metabolism with only 20% excreted as unchanged drug in the urine.[40] The half-life is about 12 hours under steady-state conditions and is not significantly altered by renal failure.[13] Moxifloxacin is reported to distribute extensively into tissues (2.45-3.55 L/kg) and demonstrates moderate protein binding (39%-52%).[40] Levofloxacin distributes extensively into multiple tissues (0.92-1.36 L/kg) and demonstrates moderate plasma protein binding (24%-38%) that is not concentration dependent.[40] In normal subjects, both glomerular filtration and tubular secretion are involved in the elimination of levofloxacin with almost no

metabolism occurring.[40] Half-life of levofloxacin is 6 to 8 hours in normal subjects and >20 hours in renal failure patients.[32] Pharmacokinetics of both moxifloxacin and levofloxacin were studied in 2 separate groups of intensive care patients receiving SLED for anuric AKI.[13] Mean blood and dialysate flow rates were 161 ± 4 mL/min. One group was given standard dose of moxifloxacin 400 mg intravenously 8 hours prior to dialysis and other group was given single dose of levofloxacin 250/500 mg intravenously 12 hours prior to dialysis. Noncompartmental pharmacokinetic analysis showed moxifloxacin mean volume of distribution was 3.8 L/kg and mean half-life was 6 hours with mean clearance of 2 to 3.1 L/h depending on the analysis method, whereas for levofloxacin the mean volume of distribution was 1.71 L/kg and mean half-life was 10.3 hours with mean clearance of 2.93 – 3.12 L/h based on the analysis method. Moxifloxacin pharmacokinetics in this study was similar to the parameters observed in healthy subjects and renal failure patients, and there was no significant impact of liver impairment on pharmacokinetics of the drug. This study recommended moxifloxacin standard dose 400 mg/d post dialysis in patients receiving SLED irrespective of hepatic impairment. Also, in this study, half-life of levofloxacin was shorter with SLED, so post dialysis administration with dosage adjustments recommended.[13] Furthermore, results of the national pharmacists survey found that the most frequently recommended regimen for levofloxacin was 500 mg every 24 hours.[36]

Trimethoprim/Sulfamethoxazole

In normal subjects both trimethoprim (TMP) and sulfamethoxazole (SMX) distribute extensively into tissues (TMP 100-120 L, SMX 12-18 L) and demonstrate moderate to high plasma protein binding (TMP 44%, SMX 70%).[41] Hepatic metabolism and renal clearance are involved in the elimination of both drugs.[41] Normal half-life of TMP and SMX is 6 to 17 hours and 9 hours, respectively, and prolonged in renal failure.[15] TMP/SMX in the setting of dialysis has not been studied well despite of its extensive usage for decades. However, pharmacokinetics of TMP/SMX was examined in a critical care patient with cANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) positive vasculitis on immunosuppressive therapy diagnosed to have pneumocystis pneumonia (PCP) and acute or chronic oliguric kidney injury requiring SLED.[15] Blood and dialysate flow rate was 170 ± 41 mL/min and TMP/SMX was administered intravenously at a dose of 15 mg/kg/d and 95 mg/kg/d, respectively, due to increased clearance by dialysis. The clearances observed were 94 ± 20.2 mL/min for TMP and 51 ± 18.8 mL/min for SMX. After the SLED, significant decrease in the plasma drug concentration observed and the clearances were higher than the reported clearances for regular hemodialysis, continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). Also, clearances were higher than the normal renal clearances, and further pharmacokinetic studies are recommended for correct and effective dosing in the setting of SLED.[15]

Colistin

Development of multidrug resistant organism lead to increased usage of colistin in critically ill patients especially in the ICU. Colistin is administered parenterally as the inactive prodrug colistimethate sodium (CMS), which is converted to the active colistin in vivo.[42] In normal subjects, about two-thirds of CMS is cleared renally and is approximately equal to the glomerular filtration rate (GFR) while nonrenal clearance of CMS includes hydrolysis which forms the active moiety.[43] High tubular reabsorption of colistin results in a low renal clearance; however, CMS excreted into the urine is also hydrolyzed to colistin in the urinary tract.[43] Normal half-life of CMS is about 2 to 3 hours and 2 to 3 days in patients with anuria.[44] The volume of distribution of colistin and CMS is approximately equivalent to the extracellular space (CMS: 14.0 L, colistin: 12.4 L) and the protein binding of colistin in critically ill patients is moderate (59%-74%).[43] Reduced dose of colistin is required in patients with renal failure as half-life of the drug increases with decreasing GFR.[16] However, pharmacokinetics of colistin in SLED is not studied except for a recent study investigating single- and multiple-dose pharmacokinetics in a patient with AKI receiving extended daily dialysis complicated by multidrug resistant Klebsiella pneumonia.[16] The mean flow rates of blood and dialysate were 191 mL/min and 121 mL/min, respectively, and the average duration of dialysis was 9.2 hours. Colistin methanesulfonate is an inactive prodrug used for intravenous injections and converts into colistin inside the body.[16] The patient was given loading dose of 6 million units followed by 9 million units/d in 3 divided doses for 9 days. The drug clearance with SLED for colistin was 54 to 71 mL/min and for colistin methanesulfonate was 25 to 62 mL/min. There was no accumulation of either colistin or its prodrug colistin methanesulfonate with the above mentioned doses of colistin. This study inferred that SLED has a greater impact on drug clearance compared with standard IHD and higher doses of colistin is required to maintain effective therapeutic blood levels. It was recommended that in patients receiving SLED for an average of 9 hours a day, 9 million units of colistin per day in 3 divided doses is sufficient.[16]

Conclusion

Pharmacokinetic principles should be taken into consideration for the appropriate dosing of drugs during SLED, yet it is vital to monitor response to drug to make sure therapeutic goals are achieved. Antibiotic dosing and timing relative to the initiation of SLED may be important to maximize either the time above the MIC (time-dependent) or the peak to MIC ratio (concentration-dependent), balancing efficacy and toxicity concerns. When the expected clinical response does not

occur, the sufficiency of drug dosing in SLED can be challenged given the lack of adequate clinical trials. It is a challenge to find therapeutic doses for antibiotics during SLED therapy because, in general, only aminoglycosides and vancomycin can be assayed in clinical laboratories. Critical care clinicians should liaise with nephrologists to make decisions regarding appropriate antibiotic dosing in patients undergoing SLED, as there is lack of guidelines and large-scale clinical trials. Future large-scale research should focus on establishing guidelines for antibiotic dosage in SLED.

Ethics Approval and Consent to Participate

This is a review article and does not involve any clinical intervention on patients.

Consent for Publication

This is a review article and does not involve any clinical intervention on patients.

Availability of Data and Materials

This is a review article, and all the data is provided in the tables 1 & 2.

Declaration of Conflicting Interests

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