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Drug dosage in continuous venoveno hemofiltration in critically ill children

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1. ABSTRACT

The dosage of drugs in patients requiring continuous renal replacement therapy need to be adjusted based on a number of variables that that affect pharmacokinetics (PK) including patient weight, CRRT modality (convention, vs. diffusion), blood and/or effluent flow, hemofilter characteristics, physiochemical drug properties, volume of distribution, protein binding and half-life as well as residual renal function. There is a paucity of data on PK studies in children with acute kidney injury requiring CRRT. When possible, therapeutic drug monitoring should be utilized for those medications where serum drug concentrations can be obtained in a clinically relevant time frame. Also, a patient-centered team approach that includes an intensive care unit pharmacist is recommended to prevent medication-related errors and enhance safe and effective medication use is highly recommended. The aim of this article is to review the current guidelines for drug dosing in critically ill children who require continuous venovenous hemofiltration.

2. INTRODUCTION

Acute kidney injury (AKI) is a common problem in pediatric patients and is associated with significant mortality and morbidity (1-4). It occurs in 5% of all hospitalized patients and up to 30% of critically ill patients (5,6). The morbidity and mortality rates are 40% and 60%, respectively in all patients admitted to the pediatric intensive care unit (7-10). The critically ill and hemodynamically unstable children with AKI are frequently treated with continuous renal replacement therapy (CRRT) (11-17). CRRT, unlike the traditional hemodialysis and peritoneal dialysis provides a slow and gentle fluid removal from body much like the native kidneys and removes inflammatory mediators of sepsis such as interleukin, TNF-alpha, and complement. CRRT also provides adequate nutritional support for the catabolic AKI patients a controlled desired fluid balance (18,19).

Many AKI patients receiving CRRT suffer from multiple organ dysfunctions and are also on various types of medications including antibiotics, anticonvulsants, anticoagulants, and cardiovascular agents. With the use of CRRT in the critically ill patients it is of the utmost importance to properly dose the multitude of drugs administered in these patients, especially those whose pharmacodynamic (PK) effects are difficult to measure.

Many guidelines for drug dosing during CRRT are extrapolated from experiences with adult chronic hemodialysis and there has been a relative paucity of data concerning PK and CRRT in pediatric patients (20). Drug properties such as protein binding, sieving coefficient, volume distribution (Vd), and half-life all influence the drug PK so dosing adjustments are variable (21,22). Drug doses used in adults cannot be directly applied to these children, as the CRRT dialysate prescription and pharmacokinetic are different in adults compared with children. The extent of drug removal is variable depending on the CRRT modality, convection or diffusion or both, patient body weight, blood flow, ultrafiltrate and dialysate

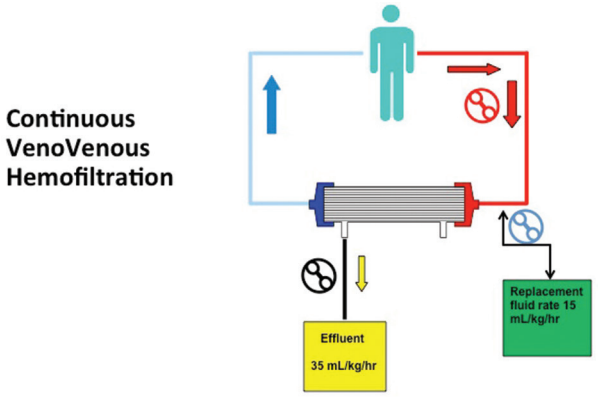

Figure 1. CVVH extracorporeal circuit with the aid of a blood pump and using venous access.

flow rates, membrane size, drugs molecular weigh, Vd, protein binding, as well as residual renal function and non-renal drug clearance. Failure to correctly dose may result in either drug toxicity or treatment failure. In order to understand the optimal drug dosing for children receiving CRRT, one must understand the pattern of water and solutes transport through a semipermeable membrane by all forms of CRRT (23). The existing FDA guidance however, does not include a recommendation for PK studies in CRRT, and the studies are not required for getting approval, so currently, no regulatory incentive exists for pharmaceutical manufacturers to study PK in CRRT during drug development (24).

To date, there are mostly sporadic post-marketing studies that exist for less than 20 percent of currently marketed drugs. It is common place to most often extrapolate dosing recommendations from PK studies that used outdated CRRT technology, from studies in ESRD patients receiving intermittent hemodialysis and adult patients, each of which typically requires lower doses than higher intensity CRRT. For example, in a recently published retrospective study by Gist *et al*, the authors discuss the use of therapeutic drug monitoring for dose adjustment of milrinone in critically ill children, including some who required CRRT (25). They reported a large variability in milrinone concentrations, which were often outside the target a range, as well as large between patient variability suggesting that dosing regimens should be individualized in critically ill patients.

This review article provides recommended CVVH dosing adjustments for drugs commonly used in critically ill children.

3. CONTINUOUS VENOVENO HEMOFILTRATION (CVVH) PRINCIPLES

CVVH is one of the most commonly CRRT modalities used for the treatment of hemodynamically unstable patients complicated with AKI, fluid overload and septic in the intensive care unit setting (16, 23,26,27). Primary therapeutic goal of CVVH is water and solute removal across a semipermeable membrane to provide fluid balance as well as control of electrolyte balance. Continuous hemofiltration with the aid of a blood pump provides solute removal by convection (Figure 1). CVVH offers high volume ultrafiltration using replacement fluid, which can be administered pre-filter or post-filter. In post-dilution the drug clearance equals the ultrafiltration rate, while in pre-dilution the replacement fluid should be considered when calculating clearance. The pump guarantees adequate blood flow to maintain required ultrafiltration rates. Venous blood access is usually jugular or subclavian using a double lumen cannula (28,29).

Because unwanted solutes are removed by taking off plasma water, increased clearances are achieved by using higher ultrafiltration rate to remove more plasma water. Compared to CVVHD therapy, CVVH provides less efficient removal of solutes of small molecular weight (<350 Daltons), but more efficient removal of solutes of larger molecular weight (30).

4. DRUG DOSING ADJUSTMENTS DURING CVVH TREATMENT

In general, drugs that are predominately removed by the normal kidneys require a dose reduction in patients with AKI (31). If CRRT is initiated, some of the drugs may be eliminated by CRRT (32-36). The extent of drug removal determines whether supplemental dosing is necessary during CRRT to avoid the drug under-dosing. Therefore, a dose adjustment is required to prevent under dosing of the medication or drug toxicity.

The impact of CRRT on drug removal is variable depending on the various techniques are used in the management of AKI, the blood flow, ultrafiltrate and dialysate flow rates, the filter, and the patients residual renal and non-renal drug clearance (37-41). Middle and large size solutes such as inflammatory mediators, myoglobin, and bilirubin can be removed more efficiently by CVVH than diffusion technique. The data suggest an early initiation of treatment and a minimum delivery dose of 25mL/Kg/h improve patient survival rate (42). Guidelines whether or not dose adjustment is required for children with AKI is provided in Table 1. The limitations of using these dosage guidelines for children include the population of neonates and infants who continue to undergo normal renal functional maturation until age two and the unreliability of a calculated GFR in the critically ill children.

Drug dosing can be calculated from the knowledge of the PK parameters of a drug including the

Table 1. Pediatric drug dosage adjustments during continuous venovenous hemofiltration*

Drug category	Protein binding (%)	SC	Vd L/kg	T1/2 h	Normal dose (GFR 100)	Dose in CVVH<1-2L/h GFR<15-30 References 21,28,29,60
Analgesic						
Acetaminophen	20-50	0.93	0.2-.4	2-3	5 mg/kg iv q8 h	No change
Acetylsalicylic	>99	50	0.25	0.8	10 mg/kg q4-6 h	No change
Codeine	7	NA	3-6	3	0.5-1 mg/kg q6 h	75% dose reduction
Ibuprofen	90-99	NA	0.14	1.8.	5-10 mg/kg q6 h	No change
Ketorolac	>99	NA	0.1-.3	5	0.25-1 mg/kg q6 h	No change
Fentanyl	80-85	0.29	2.4.	2.6.	1-5 mcg/kg q6 h	75% dose reduction
Meperidine	60-85	NA	2.4.	11	0.5-2 mg/kg infusion	75% dose reduction
Methadone	60-90	NA	4.5.	8-49	0.5 mg/kg q6 h	0.5 mg/kg q24 h
Morphine	20-35	0.65	3.3.	2.5.	0.05-.2 mg/kg iv q2-4 h	75% dose reduction
Antimicrobials						
Aciclovir	9-33	0.85	0.7	2-3	10 mg/kg iv q8 h	Normal dose iv q24 h
Amikacin[a]	<20	0.95	0.2-.7	1.6.-2.5.	20 mg/kg (max 1.5.g) iv q24 h	10 mg/kg iv q24 h
Amoxicillin	15-20	0.85	1.3.	5-20	5-15 mg/kg iv q8 h	No change
Amphotericin liposomal	90	NA	0.1-.4	6-10	3-5 mg/kg iv q24 h	No change
Ampicillin	17-20	0.8	0.32	1-1.8.	50 mg/kg iv q8 h	No change
Azithromycin	10-50	NA	NA	6-8	5 mg/kg q12	No change
Atrreonam	50-60	NA	0.25	2	80-120 mg/kg q8 h	No change
Benzylpenicillin	60	NA	0.3-.4	0.5-1.2.	25-50 mg/kg iv in q8 h	No change
Cefaclor	20-50	NA	0.24-.35	1	10-20 mg/kg iv q12 h	No change
Cefazolin	70-86	NA	0.13-.22	2	50-100 mg/kg iv q8 h	505 dose reduction
Cefotaxime	40	NA	0.3	1.5.	50 mg/kg iv q8-12 h	No change
Ceftazidine	<10	NA	0.2-.4	1	25 mg/kg iv q8 h	No change
Ceftriaxone	85-95	0.66	0.35	8	80 mg/kg (max 2g) iv q24 h	No change
Cefuroxime	33	0.66	0.19	1.5.	25-50 mg/kg iv q8 h	25-50 mg/kg iv q12-24 h
Cidofovir	<10	NA	0.3	15-25	5 mg/kg iv q 1-2 weeks	2 mg/kg iv q1-2 weeks
Ciprofloxacin	20-40	0.7	2-3	4-5	10 mg/kg (max 400 mg) iv q12 h	25% reduction q 12 h
Clindamycin	>90	0.4	0.6-1.2.	2-3	5-10 mg/kg (max 1.2.g) iv q6 h	No change
Co-amoxiclave (amoxicillin+clavulanic acid)	17-30	NA	0.2-.4	0.9	30 mg/kg (max 1.2.g) iv q8 h	50% dose reduction
Co-trimoxazole (trimethoprim+sulfamethoxazole)	50-66	NA	0.3-2.2.	5.5.-17	40-60 m h/kg ivq12 h	50% dose reduction
Erythromycin	70-95	0.3	0.6-1.2.	2	12.5.-25 mg/kg iv q6 h	No change
Flucloxacillin	95	NA	0.13	2-3	25-100 mg/kg iv q8 h	No change
Fluconazole	12	NA	0.6-1.2.	15-20	6-12 mg/kg iv q 72 h	No change
Ganciclovir	1-2	0.84	0.4-.8	3-28	5 mg/kg iv q 12 h	50% dose reduction
Gentamicin[a]	1-30	0.95	0.2-.5	1-3	7 mg/kg iv q 24 h	4 mg/kg iv q24 h
Imipenem	13-21	1	0.5	1-1.3.	15 mg/kg (max 500 mg) iv q6 h	25% dose reduction

Contd...

Table 1. *(Continued...)*

Drug category	Protein binding (%)	SC	Vd L/kg	T1/2 h	Normal dose (GFR 100)	Dose in CVVH<1-2L/h GFR<15-30 References 21,28,29,60
Isoniazid	10-15	NA	NA	2.8.	10-15 mg/kg q12-24 h	No change
Ketakonazole	85-99	NA	2-4	8	3-6 mg/kg q24 h	No change
Levofloxacin	25-38	0.8	NA	NA	5-10 mg/kg q24 h	No change
Meropenem	2	NA	0.4	1.5.-2.3.	10-20 mg/kg iv q8 h	No change
Metronidazole	<20	,8	1.1.	6-12	7.5. mg/kg (max 500 mg) iv q8 h	No change
Nafcillin	90	0.2	0.35	1	15-50 mg/kg iv q4-6 h	No change
Olfaxacillin	20-30	NA	NA	NA	15 mg/kg iv q12 h	No change
Piperacillin	20-30	NA	0.2	0.7	200 mg/kg q4 h	200 mg/kg q8 h
Rifampicin	80	0.2	0.66	1-3.8.	10 mg/kg (max 500 mg) iv q12 h	No change
Streptomycin	34	NA	NA	5-8	20-40 mg/kg iv q24 h	7.5. mg/kg q24 h
Ticarcillin	45-65	NA	0.22	1.1.	80 mg/kg (max 3.2.g) q 8 h	No change
Tobramycin	44-50	1.6.	1.6.	11	60 mg/kg iv q12 h	50% dose reduction
Vancomycin[a]	55	NA	0.4-0.7	5.6.	15 mg/kg iv q8 h	10 mg/kg iv q 12 h
Anticoagulants						
Heparin[b]	95	<0.1	1	2	10-25U/kg/ h	No change
Warfarin	>90	0.02	0.05	50	0.5-8 mg q24 h	No change
Anticonvulsives						
Carbamazepine	75-90	74	0.25	1.3.	5-10 mg/kg q12 h	75% dose reduction
Phenobarbital	30-50	0.6	0.8	80	3-7 mg/kg q24 h	10 mg/kg q 6-8 h
Phenytoin	80-90	0.1	0.6	20	3-7 mg/kg q8 h	No change
Valporic acid	80-93	0.1	0.2-1	9-16	10-30 mg/kg q12 h	No change
Antihistamines						
Cimetidine	19	0.8	1	2	4-8 mg/kg q12 h	50% dose reduction
Diphenhydramine	78	NA	3-6	5-11	1 mg/kg q4-6 h	No change
Famotidine	15-20	NA	1-1.5.	2-4	0.5 mg/kg q12 h	No change
Terbutaline	25	NA	1.6.	5.7.	0.1-.4 mg/kg/ min iv infusion	No change
Antihypertensive agents						
Amlodipine	93	NA	21	40	0.05-.17 mg/kg q24 h	No change
Capropril	30	NA	1.5.	1.5.	0.1-.5 mg/kg q6-8 h	75% dose reduction
Clonidine	20-40	0.7	2.1.	8	2.5.-5 mcg/kg q12 h	No change
Enalapril	<50	0.5	1.7.	11	0.1 mg/kg q12 h	75% dose reduction
Hydralazine	85-90					0.15 mg/kg q8 h
Isradipine	95	0.13	1.5.	1	,05-.2 mg/kg q8 h	No change
Labetalol	50				0.4-3 mg/ h iv infusion	No change
Lisinopril	25	NA	NA	5-6	0.1 mg/kg q12-24 h	0.50% dose reduction
Nifedipine	95%	0.08	1.2.	2.8.	0.25-.5 mg/kg q6-8 h	No change
Prazosin	95	0.03	0.6	2.9.	0.2-1 mg/kg q12 h	No change
Propranolol	60-90	0.07	4.3.	3.5.	0.1-1 mg/kg q6 h	No change

Contd...

Table 1. *(Continued...)*

Drug category	Protein binding (%)	SC	Vd L/kg	T1/2 h	Normal dose (GFR 100)	Dose in CVVH<1-2L/h GFR<15-30 References 21,28,29,60
Cardiovascular agents						
Amiodarone	96	0.03	61	N/A	5-10 mg/kg q 24 h	No change
Atenolol	<5	1	0.43	6	1-2 mg/kg q24 h	No change
Atropine	14-22	0.5	2.9.	2-4	0.5-1 mg q5-30 min	No change
Digoxin	20-55	0.8	6.5.	40	250 mcg q24 h	62.5.mcg q24 h
Dobutamine	NA	NA	0.2	2	2-20 mcg/kg/min iv infusion	No change
Dopamine	NA	NA	NA	5.5.	2-20 mcg/kg/min iv infusion	No change
Epinephrine	N/A	NA	<.1	<.1	0.01-1 mcg/kg/min iv infusion	No change
Milrinone	70	NA	0.38	2.3.	0.25-.75 mcg/kg/min iv infusion	0.33 mcg/kg/min iv infusion
Procanimide	15-20	NA	1.7.-2.5.	3-4	20-80 mcg/kg/min iv infusion	No change
Verapamil	90	0.13	4.3.	5	1-2 mg/kg q8 h	No change
Miscellaneous						
Aminophylline	40	0.47	NA	40	2 mg/kg q8 h	No change
Cytoxan[c]	13	0.83	0.78	7.5.	Follow protocol	50-75% dose reduction
Cyclosporine[a,c]	96	0.1	3	1	Follow protocol	No change
Dexamethasone	68	0.32	1	3	1-4 mg q6 h	No change
Hydrocortisone	70-90	NA	0.4-.7	1.7.	1-5-10 mg/kg q6 h	No change
Insulin	98	0.95	<.1	0.3	0.5-10 U/ h	No change
Mycophenolate	97	NA	91	8-16	600 mg/ m^2q12 h	No change
Sirolimus	92	NA	20	60	1 mg/ m^2q24 h	No change

*Subsequent doses should be based on the estimated ultrafiltration capacity of the CVVH. CVVH=continuous venovenous hemofiltration; SC=seiving coefficient (fraction); Vd=volume distribution; t1/2=half-time; GFR=glomerular filtration rat; iv=Intravenous; NA=not available; [a]Levels need to be checked daily; [b]Dose need to be adjusted according to APPT measured q12-24h; [c]According to protocol

drug distribution, elimination within the body and the desired drug concentration in plasma (43). In the case of patients with AKI being treated with CRRT, clearance will depend on a combination of CRRT clearance, residual renal function and non-renal clearance. Both the volume of distribution and the non-renal clearance may be changed by AKI and critical illness In general, drug dosing during CRRT should follow the following pharmacokinetic parameters (44-50).

4.1. Volume of distribution (Vd)

The dose administered divided by the final plasma concentration of drug yields a number with units of volume, called the "volume of distribution."

Vd (L/Kg) = loading dose (mg/Kg)/concentration (mg/L).
Loading dose (LD) mg/kg = Vd × serum concentration (mg/dL)

Fluid overload and extracellular fluid volume expansion increase volumes of distribution for hydrophilic drugs, such as aminoglycosides. In contrast, extracellular volume contraction decreases volume of distribution for hydrophilic drugs.

4.2. Protein binding (Pb)

Pb describes the bound fraction of drug but also determines free fraction of drug available for pharmacological action. It is the single major determinant of clearance in patients on CRRT at a given rate, because only the unbound fraction is available to be filtered. Pb is decreased in patients with nephrotic syndrome and increases during albumin administration. Other factors that may affect pb in the critically ill children include pH, heparin therapy, hyperbilirubinemia, uremia, blood free acid concentration and presence of drugs that are competitive displacers (51-53).

4.3. Sieving coefficient (SC)

SC is the ratio of drug concentration on the filtrate side of the membrane to drug concentration in the

blood passing through the filter. The SC vales can vary from zero for drugs that cant not be filtered to one for drugs, which are freely filtered. The major determinant of the SC is the proportion of the plasma protein binding, because the drug that is bound to plasma protein is not available for filtration.

4.4. Plasma clearance (Cl)

In consideration of drug Cl, metabolism of the drug is usually significant and sometimes dominates elimination of drug from plasma. The drug may also be secreted in bile and eliminated in stool. Drug Cl (mL/min) = Volume (mL)/Time (min); where Cl=describes clearance of drug (volume) from the body per unit time in min. Drug clearance decreases in patients with oliguric AKI.

4.5. Maintenance dose (MD)

MD/mcg = CL (mL/min) x serum concentration (mcg/mL) x dosing interval (min)

Half-life ($t_{1/2}$) =0.6.93 x ke hours^{-1},

where ($t_{1/2}$) is the time in hours that it takes for the serum concentration of a drug to be reduced by 50% and ke hours^{-1} =Vd (L) x CL (mL)/min. ($t_{1/2}$) increases in oliguric AKI and shock syndromes.

5. CRRT IMPACT ON PK PARAMETERS

Prescription variables that may affect PK include patient seize, organ function, volume status, physiochemical drug properties, CRRT modality (convective vs. diffusive clearance routes), blood and/or dialysate flow and solute clearance, and hemofilter characteristics (54-56).

AKI affects both distribution and elimination of many drugs (57-63). CRRT also impacts on PK parameters in many ways. Replacement fluids may affect drug removal by influencing the drug concentration within the filter (15). Usual circuit priming volume ~100-150 mL can increase Vd. Tubing and membrane filter bind drug and increases Vd. The use of higher blood flow rate (>3-5mL/Kg/min) can also lead to increased CL. The use of higher ultrafiltration rate ~ filter replacement fluid rate (>35-40mL/Kg/h or 2.5.L/m^2/h) also lead to increased Cl.

The correct drug dosing should consider not only the extracorporeal drug removal, type of filter membrane but also residual renal and non-renal clearance and drug molecular weight, protein binding information and volume of distribution to avoid medications error. The ideal drug to be removed by CVVH that requires a dose adjustment has: a low protein binding, a low volume of distribution, and a low non-renal clearance.

Depending on the drug, it may be more appropriate to shorten the dosing interval or to increase the dose. Example, in oliguric AKI patients a very small single daily dose of aminoglycosides can be used to achieve peak concentrations and to avoid toxic side effects. After CRRT initiation, it is recommended to increase the single daily dose to achieve peak levels while lowering aminoglycosides levels to low trough concentration and avoiding the risk of side effects. In contrast, the bactericidal effect of β-lactam antibiotics (penicillins and cephalosporines) correlates with constant plasma levels above the minimal inhibitory concentrations of the bacteria and side effects may occur if high peak concentrations are reached with use of high single doses. In these drugs it may be useful to shorten the dosing intervals instead of increasing the individual dose (Table 1).

All β-lactams are small size (molecular weight <800 Daltons) have volume distributions >0.3. L/kg and protein bounding fraction <10% except for oxacillllin and ceftriaxone are not clinically significant. They undergo significant extracorporeal clearance during CVVH (45-50).

Meropenem, and aminoglycosides also have pharmacokinetic properties such as low molecular weight, small volume of distribution and negligible protein binding. They are easily filtered due to its low molecular eight, low volume of distribution and low protein binding. In contrast, quinolones (ciprofloxacin and levofloxacin) with molecular weight about 370 Daltons, volume of distribution 1.2.-1.8. L/kg and protein binding of 25-50% are less liable to clearance by CVVH (48-50).

Glycopeptides (vancomycin) has a large molecular weigh nearly 1550 Daltons with volume distribution of 0.3.8 L/kg and protein binding of 30% (57). The normal function kidneys clear about 70% of the drug. The clearance rates of vancomycin in patients on CAVVH are compatible with clearance in patients with GFR >50 mL/min.

As a general rule, because of the presence of a positive fluid balance in the early stages of AKI, the dosing regimen for many drugs, especially antimicrobial agents, should be initiated at normal or near-normal recommended dosage. In general, a loading dose that will achieve the target serum concentrations based on the expected volume of distribution should be given and no adjustments need to be made for residual renal function.

When possible, therapeutic drug monitoring should be utilized for those medications where serum drug concentrations can be obtained in a clinically relevant time frame. A patient-centered team approach that includes an ICU pharmacist is recommended to prevent medication-related errors and enhance safe

and effective medication use is highly recommended. Clinical pharmacist provides excellent services including collecting patient data, estimating creatinine clearance and advising the physician to adjust medication dosages based on the creatinine clearance.

6. SUMMARY AND PERSPECTIVE

Drug dosing must be adjusted in children receiving CVVH due to its effects on drug PK. Drug properties such as protein binding, sieving coefficient, volume distribution, and half-life all influence the drug PK so dosing adjustments are variable. Both the volume of distribution and half-life of several drugs are markedly increased in the presence of AKI and thus larger loading doses may need to be administered to achieve the target serum concentrations. Therapeutic drug monitoring should be utilized for those medications where blood drug concentrations can be obtained in a clinically relevant time frame.

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Abbereviations: CVVH, Continuous venoveno hemofiltration; PK, Pharmacokinetics; AKI, Acute kidney injury

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