Dosing Recommendations for Continuous Venovenous Hemodiafiltration with AN69 Filter Membranes and Prismaflex Dialyzers

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ABSTRACT

Background: Continuous renal replacement therapy is used to manage fluid and solute imbalances in critically ill patients but may affect the clearance of concurrently administered drugs. The impact of continuous renal replacement therapy on pharmacokinetics has been summarized, but previous reports have included studies involving various modes of therapy, filter membranes, and brands of dialyzers, which makes it difficult to apply the recommendations to individual patients. In Canada, continuous venovenous hemodiafiltration (CVVHDF) with a Prismaflex dialyzer machine (Gambro, Saint-Léonard, Quebec) and AN69 filter membranes is the most common mode of continuous renal replacement therapy for critically ill patients.

Objective: To develop a set of dosage recommendations for commonly encountered medications used in treating critically ill patients who are undergoing CVVHDF with a Prismaflex dialyzer and AN69 filter membranes.

Methods: A literature search was conducted to identify studies of the pharmacokinetics and disposition of drugs in patients undergoing CVVHDF via a Prismaflex dialyzer (sold under 3 brand names: Gambro, Hospal, and Prima) equipped with polyacrylonitrile (AN69) filter membranes. From each study, the mean total clearance of each study medication during CVVHDF was extracted and compared with clearance of the drug in patients not undergoing CVVHDF, to produce dosage guidelines for patients undergoing CVVHDF.

Results: A total of 22 studies of 14 medications were included in the final review. For most of the drugs, the total clearance during CVVHDF was less than clearance in patients whose renal function was presumed to be normal. Fluconazole and moxifloxacin had greater total clearance during CVVHDF, but a dose adjustment during CVVHDF was deemed necessary only for fluconazole.

Conclusions: Dosing recommendations were created for concurrently administered drugs for patients undergoing treatment with this particular CVVHDF equipment. Patient-specific factors and clinical judgement should also be taken into account.

Key words: continuous renal replacement therapy, continuous venovenous hemodiafiltration, Gambro, polyacrylonitrile (AN69) filter membranes, critical illness, hemodiafiltration

RÉSUMÉ

Contexte : Le traitement continu de remplacement de la fonction rénale est utilisé pour rétablir l'équilibre hydro-électrolytique chez les patients gravement malades, mais il peut modifier la clairance des médicaments administrés en concomitance. L'effet du traitement continu de remplacement de la fonction rénale sur le comportement pharmacocinétique a fait l'objet de synthèses, mais ces rapports antérieurs ont compilé des études ayant eu recours à divers modes de traitement, membranes filtrantes et marques de dialyseurs, ce qui rend difficile l'application des recommandations à des cas particuliers. L'hémodiafiltration vénoveineuse continue (HDFVV) au moyen du dialyseur Prismaflex (Gambro, Saint-Léonard [Québec]) et de membranes filtrantes AN69 constitue la méthode de remplacement de la fonction rénale la plus courante chez les patients gravement malades au Canada.

Objectif : Créer une série de recommandations posologiques pour les médicaments les plus couramment utilisés dans le traitement des patients gravement malades sous HDFVV au moyen du dialyseur Prismaflex et de membranes filtrantes AN69.

Méthodes : Une recherche bibliographique a été effectuée pour déterminer les études du comportement pharmacocinétique et du devenir des médicaments chez les patients sous HDFVV au moyen du dialyseur Prismaflex (vendu sous trois noms de marque : Gambro, Hospal et Prisma) muni de membranes filtrantes de polyacrylonitrile (AN69). Pour chacune des études, on a recensé la clairance moyenne totale de chaque médicament à l'étude chez les patients sous HDFVV et on l'a comparée à sa clairance chez les patients qui n'étaient pas sous HDFVV, pour ainsi produire des lignes directrices sur la posologie des médicaments utilisés chez les patients sous HDFVV.

Résultats : Au total, 22 études de 14 médicaments ont été incluses dans l'analyse finale. Pour la plupart des médicaments, la clairance totale durant l'HDFVV était inférieure à la clairance chez les patients dont la fonction rénale était supposément normale. Le fluconazole et la moxifloxacine avaient une clairance totale plus importante durant l'HDFVV, mais un ajustement de la dose durant l'HDFVV a été jugé nécessaire seulement pour le fluconazole.

Conclusions : Des recommandations posologiques ont été créées pour les médicaments administrés en concomitance avec l'HDFVV effectué avec ce dialyseur particulier. Les facteurs spécifiques au patient et le jugement du clinicien doivent également être pris en compte.

Mots clés : traitement continu de remplacement de la fonction rénale, hémodiafiltration vénoveineuse continue, Gambro, membranes filtrantes en polyacrylonitrile (AN69), maladies graves, hémodiafiltration

[Traduction par l'éditeur]

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INTRODUCTION

Continuous renal replacement therapy is increasingly used as an effective method of extracorporeal blood purification in critically ill patients.[1,2] The indications for renal replacement therapy include acute or chronic kidney disease, refractory metabolic acidosis, multiple organ system failure, or refractory volume overload.[3] Continuous renal replacement therapy may be continued for several days after initiation and therefore often occurs concurrently with drug therapy. In addition to removing uremic toxins and other undesirable solutes, continuous renal replacement therapy also serves as an alternative pathway for drug removal and contributes to total body clearance of drugs. This extracorporeal clearance further complicates dosing for critically ill patients with severe kidney disease. For many of the medications that may be administered during this procedure, the optimal dosage regimen is unknown, which leads to bedside estimation of dosage by clinicians. However, if the magnitude of the effect of renal replacement therapy is estimated incorrectly, there is a risk of overdosing or subtherapeutic dosing. Therefore, collection of data from studies of the disposition of drugs administered during this procedure would be valuable in developing dosing guidelines.

The disposition of drugs in patients undergoing continuous renal replacement therapy has been reviewed in several documents and standard references.[1,2,4] However, these publications incorporate data from studies using different modes of therapy, such as continuous venovenous hemodialysis, continuous venovenous hemofiltration, and continuous venovenous hemodiafiltration (CVVHDF). In addition, the studies used different types of filter membranes and dialyzer brands. Consequently, it is difficult to apply dosing recommendations to a clinical setting in which a specific therapeutic process, brand of dialyzer, and membrane are being used.

The most common mode of renal replacement therapy is CVVHDF. This process optimizes clearance of small and large solutes by simultaneous diffusion (i.e., dialysis, the movement of solutes from an area of higher to lower concentration) and convection (i.e., hemofiltration, the movement of solutes with the flow of water, also known as "solvent drag"). CVVHDF requires use of a dialysate fluid for diafiltration and a replacement fluid for hemofiltration. The Gambro Prismaflex systems account for 99% of the Canadian market (L. Magee, Gambro Acute Division, personal written communication, November 22, 2007). The acrylonitrile (AN69) filter membrane is the most documented biocompatible membrane for continuous renal replacement therapy and is the most frequently used membrane in Canadian hospitals.[3]

The purpose of this literature review was to develop a list of dosage recommendations for medications commonly used for treating critically ill patients who are undergoing concurrent CVVHDF with AN69 filter membranes and a Prismaflex dialyzer (Gambro, Saint-Léonard, Quebec).

METHODS

The MEDLINE (1950 to January week 1, 2008) and EMBASE (1980 to 2008 week 1) databases were searched to identify articles reporting studies of the pharmacokinetics and disposition of drugs in patients undergoing continuous renal replacement therapy. The following terms were used for the MEDLINE search: "AN69", "hemofiltration", "hemodialfiltration", "continuous venovenous hemodialysis", "renal replacement therapy", "CRRT", "critical illness", and "intensive care units". Articles similar to "Pharmacokinetics and antimicrobial dosing adjustment in critically ill patient during continuous renal replacement" were assessed. The search terms used for the EMBASE search were "an69", "continuous renal replacement therapy", and "hemofiltration", with articles similar to "Pharmacokinetics and antimicrobial dosing adjustments in critically ill patient during continuous renal replacement therapy" being assessed. The reference lists of any identified articles were searched manually for additional articles applicable to this review. The local representative for the manufacturer of the target filter, Gambro (Saint-Léonard, Quebec), was contacted to obtain background information and to request access to any unpublished studies.

Identified articles were evaluated to determine if the studies had involved patients undergoing CVVHDF. Data that could not be specifically linked to CVVHDF were excluded. The study had to have used polyacrylonitrile (AN69) membranes and a Prismaflex dialyzer (sold under 3 brand names: Gambro, Hospal, Prisma). From studies that met these criteria, the following data were extracted if available: predilution rate of hemodiafiltration (L/h), ultrafiltration rate (L/h), postdilution rate (L/h), dialysate rate (L/h), blood speed (mL/min), total clearance (mL/min), clearance due to continuous renal replacement therapy (mL/min), and elimination constant, K_e (h^{-1}). In studies reporting data for several membrane types or modes of continuous renal replacement therapy, data were collected as the means for individual patients who met the aforementioned criteria. If the elimination constant was not provided, it was calculated from the following pharmacokinetic equation: $K_e = 0.693/t_{1/2}$.

For medications covered by studies meeting the inclusion criteria, a second literature search was performed for each drug to determine its disposition in healthy people with normal renal function. Reference lists in MICROMEDEX drug monographs were assessed for relevant primary pharmacokinetic studies and drug dosing in critically ill patients. Searches were conducted of the PubMed, MEDLINE, and EMBASE databases, and Google Scholar was used to search the Internet, using the medication name and the following search terms:

Table 1. Pharmacokinetic Parameters for Patients Undergoing Continuous Venovenous Hemodiafiliation with Prismaflex Dialyzer and AN69 Membrane Filters*

Drug and Dose Regimen	Hemodiafiltration Rate (L/h)				Blood Speed (mL/min)	Clearance (mL/min)		K_e (h^{-1})
	Before Dilution	Ultrafiltration	After Dilution	Dialysate		Total	CRRT	
Amikacin								
500 mg x 1 dose[8]		1		1	100	28.5 ± 4.6	16.9 ± 6.0	0.0613 ± 0.462†
Cefepime								
1 or 2 g q24h[9]		1.046 ± 0.240‡	NR	0.957 ± 0.081‡	150	47 ± 0.12	26 ± 5	0.081 ± 0.50†
2 g IV q8h[10]		1.64	NR	0.5	150	98.3	31.5	0.136†
Ceftazidime								
1 g q6h[11]	1	0.5–1		1	140	53.8‡	28.8‡	0.087†‡
2 g IV loading dose over 3 min, then 3 g continuous infusion over 24 h, beginning immediately after loading dose[12]		1.5	NR	1	150	62.4 ± 4.8	33.6 ± 4	0.19 ± 0.63†
Ciprofloxacin								
200 mg q8h[13]	2	2		1	200	203 ± 72	37 ± 7	0.074 ± 0.14†
400 mg q12h to q24h[14]		1.04‡	NR	0.96‡	150	146‡	21‡	0.083†‡
CMS or colistin sulphate (metabolite) 150 mg (2.46 mg/kg IBW) q48h[15]		2	2	1	200	48.7	CMS: 11.2 Colistin: 11.9	CMS: 0.101† Colistin:0.092†
Enoxaparin								
40 or 60 mg/day[16]		1.5–2	NR	1	150–200	NR	10.4–23.6	–
Fluconazole								
400–800 mg/day[17]	1	1.158 ± 0.0905		1	90	37.9 ± 4.4	30.5 (6.0)	0.0291‡
Imipenem								
500 mg q8h to q12h[18]		1.16	NR	0.923	150–200	178 ± 18	57 (28)	0.271 ± 0.436†
Levofloxacin								
250 or 500 mg q24h to q48h[14]		1.11	NR	1.03	150–200	61.4‡	21.6‡	0.0373†‡
500 mg/day (or 125 mg/day)[19]	1	1.19‡		1	90	54.04 ± 23.15	26.05 ± 4.66	0.0241 ± 0.154†
Meropenem								
0.5, 1, or 2 g q6h to q8h[20]		1.22‡		0.92‡	100–200	179.3‡	28.17‡	0.212†‡
1 g q12h[21]		1.741		1.6	100	53.1 ± 17.0	30.4 ± 2.0	0.153†
1 g q12h[22]		1–2	1–2	1–1.5	150	78.7‡	38.9‡	0.168‡
Variable dosing[23]:	0.5 ± 0.3	0.13 ± 0.07		1.2 ± 0.3	119 ± 15	4.5	1.62	0.135
• 500 mg or 1000 mg q8h (n = 2 patients)								
• 500 mg q12h (n = 4)								
• 1000 mg q12h (n = 9)								
Moxifloxacin								
400 mg daily[24]	1	1.01 ± 0.07		1	150	318.2 ± 137	27.2 ± 5.5	0.0702 ± 0.213†
Netilmicin								
150 mg q12h[25]		0.15	NR	0.875	130	44.0 ± 2.0	NA	0.11 ± 0.01‡
Vancomycin								
7.5 mg/kg[26]		0.474 ± 0.120		0.5	100–150	38.9 ± 4.3	4.2 ± 1.3	0.0499 ± 1.0†
750 mg q12h[27]	2	2		1	200	42 ± 12	30 ± 6.7	0.0444 ± 0.0797†
Voriconazole								
6 mg/kg twice at 14-h interval, then 4 mg/kg q12h[28]	0.5			1	120	338	20	0.0506
6 mg/kg twice daily for 1 day, then 4 mg/kg q12h[29]	1			1	150	215 ± 112	18 (5)	0.0471 ± 0.107†

CMS = colistimethate sodium, CRRT = continuous renal replacement therapy, IBW = Ideal body weight, K_e = elimination constant during CRRT, NR = not reported.
*Data are presented as mean ± standard deviation (if standard deviation was available in the published study). If only the range was provided, the range was extracted instead of the mean.
†Calculated from half-life ($t_{1/2}$).
‡Calculated from data tables of individuals.

"healthy volunteers", "healthy subjects", and "pharmacokinetics". Data were collected for the pharmacokinetic parameters total clearance and elimination constant. Where possible, these data were obtained from studies that investigated the drug in the same dosage form (e.g., IV administration) as the dosage form commonly used for critically ill patients.

RESULTS

Twenty-five studies were identified that included data on the pharmacokinetics of medications for patients undergoing CVVHDF with AN69 filter membranes and a Gambro, Hospal, or Prisma dialyzer. One study on cefepime was excluded because the data indicated that CVVHDF clearance was greater than total body clearance for the study population, an impossible result. The methods used for studies of glutamine, folic acid, and pyridoxal-5′-phosphate did not allow determination of pharmacokinetic parameters specific to CVVHDF, and these studies were also excluded.[5,6] Therefore, a total of 22 studies[8-29] of 14 medications were included in the final review (Table 1).

For each of the 14 medications, the total clearance and elimination constant (K_e) for healthy patients were extracted (Table 2), as well as the usual dosing for critically ill patients (Table 3). For drugs that were reported in more than one study, for which more than one value for total clearance was found, the mean total clearance was calculated. The mean total clearances for each medication in healthy patients and in patients undergoing CVVHDF were used to generate dosage adjustments for patients undergoing CVVHDF (Table 3). For most drugs, the total clearance during CVVHDF was less than the clearance in normal patients with presumed normal renal function. Two exceptions were fluconazole and moxifloxacin, which had greater total clearance during CVVHDF; however, a dose adjustment during CVVHDF was deemed necessary only for fluconazole.

DISCUSSION

For many medications, the effect on drug dosing regimens of clearance due to continuous renal replacement therapy is unknown. The risk of toxic effects because of drug accumulation due to overestimation of clearance and the risk of therapeutic failure due to underestimation of extracorporeal drug clearance are major concerns for critically ill patients undergoing such

Table 2. Pharmacokinetic Parameters in Healthy Patients

	Mean ± SD or Range*	
Drug	**Total Clearance (mL/min)**	**K_e (h^{-1})**
Amikacin[30]		
7.5 mg/kg	126.7 ± 16.7	0.742 ± 0.246
15 mg/kg	112.8 ± 9.2	0.62 ± 0.088
Cefepime[31,32]	125–141	0.316†
Ceftazidime[33,34]	114[33,34]	0.478†[33] 0.35 ± 2.77[34]
Ciprofloxacin[35]	567	0.173†
CMS or colistin sulphate[36]	CMS: 112	CMS: 0.335† Colistin sulphate: 0.166
Enoxaparin subcutaneous[37]		0.169†
20 mg x 2 doses	16.67 ± 5.50	
40 mg x 1 dose	13.8 ± 3.2	
Fluconazole	28[38] 21.03 ± 5.07[38]	0.0187 – 0.0224†[39] 0.04 ± 0.01[40]
Imipenem	208.1[41,42]	0.745† ± 7.7[41] 0.636† ± 1.414[42]
Levofloxacin[43]	167.4	0.100†
Meropenem (elderly patients)[44]	139 ± 20.0	0.548 ± 0.076
Moxifloxacin[45]	248 ± 20	0.0529 ± 0.654†
Netilmicin	91 ± 13.9[46]	0.347† ± 3.5[46] 0.222‡ [47]
Vancomycin	81.2‡[48]	0.0719 – 0.147†[48] 0.115 – 0.173†[49] 0.063 – 0.139†[50]
Voriconazole	277[51] 233–583[52]	0.104[51] 0.115†[52]

CMS = colistimethate sodium, K_e = elimination constant, SD = standard deviation.
*Data are presented as mean ± standard deviation (if standard deviation was available from the published study). If only the range was provided, the range was extracted instead of the mean.
†Calculated from $t_{1/2}$.
‡Calculated from data tables of individuals.

Table 3. Dosing Recommendations for Continuous Venovenous Hemodiafiltration (CVVHDF) Based on Total Clearance with Prismaflex Dialyzer and AN69 Membrane Filters

Drug	Factor on Which Killing is Dependent	Total Clearance (mL/min)		Dosing	
		Normal	CVVHDF	Usual	CVVHDF
Amikacin	Concentration	120	28	15 mg/kg per day IV in 2 or 3 divided doses[53]	4 mg/kg per day IV in 1 dose*
Cefepime	Time	133	73	2 g IV q12h[54]	Loading dose 2 g IV, then 1g IV q12h
Ceftazidime	Time	114	58	2 g IV q8h[55]	Loading dose 2 g IV, then 1g IV q8h
Ciprofloxacin	Concentration	567	174	400 mg IV q8h to q12h[56]	400 mg IV q24h
Colistemethate sodium	Concentration	112	49	5 mg/kg IV in 2 or 3 divided doses[57]	2.5 mg/kg IV q24h
Enoxaparin	NA	15	17†	30 mg SC q12h[58]	30 mg SC q12h
Fluconazole	NA	25	38	400 mg IV daily[59]	600 mg IV daily
Imipenem/cilastin	Time	208	178	500 mg IV q6–8h[60]	500 mg IV q8h
Levofloxacin	Concentration	167	58	750 mg IV daily[61]	Loading dose 750 mg, then 250 mg IV daily
Meropenem	Time	139	79	1 g IV q8h[62]	Loading dose 1 g IV, then 500 mg IV q8h
Moxifloxacin	Concentration	248	318	400 mg IV q24h[45]	400 mg IV q24h
Netilmicin	Concentration	91	44	7.5 mg/kg per day IV in 3 equal doses q8h; reduce dose to 6 mg/kg per day or less as soon as clinically indicated[63]	4 mg/kg per day IV in 3 equal doses q8h; reduce dose to 3 mg/k per day or less as soon as clinically indicated
Vancomycin	Time	81	40	30 mg/kg per day IV in 2 to 4 divided doses[64]	Loading dose 25 mg/kg x 1 dose, then 15 mg/kg per day IV once daily*
Voriconazole	NA	342	276	6 mg/kg IV q12h for 2 doses, followed by 4 mg/kg IV twice daily[65]	5 mg/kg q12h IV for 2 doses, followed by 3 mg/kg twice daily

NA = not applicable.
*Lack of data regarding pharmacokinetic monitoring in CVVHDF studies. Trough plasma concentration at steady state (e.g., before third dose) likely reasonable if monitoring of plasma concentration is indicated (e.g., for prolonged therapy)
†Using continuous renal replacement therapy clearance; total clearance was not reported.

therapy. This study provides an initial dosing guide for selected medications based on studies involving patients undergoing CVVHDF with a Prismaflex dialyzer and AN69 filter. These dosing recommendations will not necessarily be applicable to other types or brands of filters, which may have different physiochemical properties and therefore different rates of drug filtration.

Current guidelines for treatment of sepsis recommend that initial empirical anti-infective therapy be administered at doses that will penetrate to the presumed septic source at adequate concentrations.[7] The guidelines also recommend that patients receive a full loading dose.[7] Therefore, the dose adjustments for anti-infectives during CVVHDF shown in Table 3 are based on more aggressive dosing for serious infections in patients not undergoing CVVHDF and are intended to avoid subtherapeutic concentrations.

Several assumptions were made in preparing the dosing recommendations. It was assumed that the volume of distribution was the same in critically ill patients and those who were not critically ill. This assumption may frequently be incorrect, but the variability in the magnitude of any increases in volume of distribution and rate of return to normal volume of distribution makes it impossible to accurately estimate the impact on pharmacokinetics. This assumption allowed recommendations for loading doses for selected antibiotics to ensure adequate plasma concentrations with the first dose. If the drug therapy is initiated before CVVHDF, loading doses are not necessary. Recommendations for adjustment from recommended maintenance dose schedules were based on the need to avoid accumulation of the drug or unwanted rapid clearance resulting in prolonged periods of subtherapeutic plasma concentrations. The dose recommendations for antibiotics took into consideration the pharmacodynamic parameter of concentration-dependent killing versus time-dependent killing.

Another consideration in the use of these dosing guidelines is that many patients in the studies included in this review had severe kidney disease with minimal intrinsic kidney function. For critically ill patients with normal kidney function or mild kidney disease for whom CVVHDF is used for clearing acid or exogenous toxins, Table 1 provides the clearance of drugs

strictly by the dialyzer. Depending on the degree to which the dialyzer clears the drug, clinicians can assess whether dose adjustments are necessary. If the CVVHDF process is interrupted and the downtime is anticipated to be longer than 24 h, drug doses should be adjusted according to residual kidney function. The published data do not allow assessment of the magnitude of drug clearance with poorly functioning filters, as is frequently encountered when the filter begins to clot. Clinicians should estimate the potential for drug accumulation and associated toxic effects as filter efficiency declines.

Because of the methods used, this review had several limitations. Pharmacokinetic studies that fulfilled the stated inclusion criteria were limited in number, and only a modest number of medications could be covered by this review. No unpublished studies (i.e., studies not found in the search databases) were identified. The ability to conclusively recommend doses for individual patients is limited, because the pharmacokinetic parameters were extracted from studies with limited numbers of patients and large interpatient variability. This variability extended to the characteristics of patients within studies, who had a wide range of medical conditions, reasons for admission to critical care units, concurrent medications, severity of illness, and residual kidney function. Although calculation of the mean total clearance may minimize the impact of such variability, clinicians should appreciate these limitations when extrapolating recommendations to individual patients with characteristics different from those of patients in the included studies. Furthermore, the blood flow rates and dialysate rates used in the CVVHDF process varied among the studies. It was not possible to quantify the potential impact of these variations on clearance. Table 1 provides the parameters of the renal replacement therapy in the cited studies, which clinicians may need to take into consideration if they differ from those typically encountered in their own clinical practices.

For the drugs listed, additional studies with larger numbers of patients might confirm the pharmacokinetic parameters previously determined. In addition, pharmacokinetic studies of other medications that meet the aforementioned criteria but are not listed here are warranted.

Despite these limitations, the dosing recommendations in Table 3 represent the most up-to-date evidence-based estimations of initial dose regimens for the listed medications for patients undergoing CVVHDF with a Prismaflex dialyzer and AN69 membrane filters. Any clinician using the dose recommendations in Table 3 should recognize that these are intended only as a guide, and the determination of dose regimens for an individual patient should involve consideration of patient-specific factors and clinical judgement. Monitoring of efficacy and toxicity is necessary.

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