ANNOTATED BIBLIOGRAPHY

Drug Dosing During Continuous Renal Replacement Therapies

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Continuous renal replacement therapies (CRRT) are used to manage fluid overload and/or renal failure. The continuous nature of the fluid and solute removal has less impact on hemodynamic variables in critically ill patients, making CRRT preferred over intermittent hemodialysis for some patients in the intensive care arena. The impact of CRRT on drug removal is variable depending on the CRRT modality, the ultrafiltrate and dialysate flow rates, the filter, and the patient's residual renal function; all of these may change from patient to patient or even in the same patient depending on the clinical status. However, CRRT modalities are generally more efficient than intermittent hemodialysis at drug removal, in some cases approximating or even exceeding normal renal function, resulting in a significant risk of subtherapeutic dosing if conventional hemodialysis dosing recommendations are followed. This annotated bibliography provides a summary of publications analyzing drug removal during CRRT, including CRRT settings and drug clearance values found in each study. Caution is warranted as findings from one study may not be generalizable to all patients due to the many factors that influence drug removal. Serum drug concentrations should be monitored when available, and patient clinical status is exceedingly important for following expected and unexpected responses to drug therapies. Reviews on general drug dosing calculations in CRRT are available elsewhere.

KEYWORDS renal replacement therapies, hemodialysis, hemofiltration, renal failure

J Pediatr Pharmacol Ther 2008;13:99-113

This is an update of a bibliography by Mouser JF, Thompson JB. Drugs removed by renal replacement therapies. J Pediatr Pharmacol Ther 2001;6:79-87.

AMIKACIN

Tian Q, Gomersall CD, Ip M, et al. Adsorption of amikacin, a significant mechanism of elimination by hemofiltration. Antimicrob Agents Chemother 2008;52:1009-1013.

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Amikacin adsorption by hemofilter membranes was studied using an *in vitro* model of CVVH. Low hemoglobin and low albumin concentrations in the blood mixture were chosen to simulate critically ill patients. The CVVH settings were as follows: BFR, 200 mL/min; UFR

ABBREVIATIONS AUC, area under the curve; BFR, blood flow rate; CL_{TOTAL}, total clearance; CL_{CRRT}, clearance due to CRRT; Cmax, maximum serum concentration; Cmin, minimum serum concentration; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; DFR, dialysate flow rate; IV, intravenously; MIC, minimum inhibitory concentration; MIC_{90}, minimum concentration required to inhibit 90% of organisms; UF, ultrafiltrate; UFR, ultrafiltration rate; Vd, volume of distribution

1000 mL/hr. Two types of filters were studied: polyacrylonitrile [2 sizes] (0.6 m^2 Multiflow 60, Hospal, Meyzieu, France; 0.9 m^2 Multiflow 100, Hospal) and polyamide (0.6 m^2 Hemofilter 6S, Gambro, Hechingen, Germany). Pertinent findings included the following: amikacin is significantly adsorbed by polyacrylonitrile filters; polyamide filters adsorb much less amikacin. The adsorption is rapid (within 30 minutes of the dose), irreversible, and does not appear to reach a cumulative limit. Factors that did not affect adsorption were hemofilter surface area and blood pH. The considerable adsorption of amikacin (115 mg or more after a dose; 547 mg or more after repeated doses) has the potential to greatly impact the peak serum concentration achieved, and, therefore, bacterial killing. The authors recommend waiting at least 30 minutes following dose infusions to obtain serum concentration data.

AMPHOTERICIN B LIPID COMPLEX

Bellman R, Egger P, Djanani A, et al. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous veno-venous haemofiltration. Int J Antimicrob Agents 2004;23:80-83.

Two critically ill adults receiving amphotericin B lipid complex and CVVH underwent pharmacokinetic analyses. CVVH settings were as follows: UFR 1980 mL/hr, polysulfone filter, replacement solution delivered via the predilution mode. Multiple arterial blood and ultrafiltrate samples were analyzed for drug concentrations. Both patients received amphotericin B lipid complex at approximately 5 mg/kg/day. Pertinent findings included the following: concentration-time profiles were similar during and after CVVH; sieving coefficient in each patient was 0.4 and 0.1; Vd was 9.13 L/kg; drug adsorption to the hemofilter membrane was minimal (less than 0.15% of the dose). The authors concluded that standard doses of amphotericin B lipid complex can be administered during CVVH.

CEFEPIME

Isla A, Gascón AR, Maynar J, et al. Cefepime and continuous renal replacement therapy (CRRT): *In vitro* permeability of two CRRT membranes and pharmacokinetics in four critically ill patients. Clin Ther 2005;27:599-608.

This study analyzed both *in vitro* and *in vivo* pharmacokinetics of cefepime during CRRT. The *in vitro* portion of this study examined cefepime's permeability to 2 membranes (AN69 and polysulfone); cefepime was infused at 150 mL/min during CVVH mode with UFR 1500 mL/hr and during CVVHD mode with DFR 1500 mL/hr. Prefilter and UF cefepime concentrations were obtained. In both modes, replacement fluids were administered prefilter. The authors found that the sieving coefficient (CVVH mode) and saturation coefficient (CVVHD mode) were both 1; there was no difference between the 2 membranes. The authors also concluded that clearance depends on flow rates.

The *in vivo* portion studied 4 critically ill adults receiving cefepime 2 g IV q 8 hr. CRRT modes were CVVH (n = 2) and CVVHDF (n = 2). For all patients, the UFR was 1000 to 2100 mL/hr and replacement fluids were administered prefilter. The 2 patients receiving CVVHDF had DFR of 500 to 1000 mL/hr. Pertinent findings included the following [mean ± SD]: CL_{TOTAL} was 111.5 ± 43.1 mL/min; $\%CL_{CRRT}$ was 29% ± 16.8%; Vd 0.6 ± 0.3 L/kg; time above MIC_{90} was 100% of the dosing interval. The authors concluded that CVVHDF provided higher CL_{CRRT} due to the higher combined flow rates (UFR + DFR).

Malone RS, Fish DN, Abraham E, et al. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother 2001;45:3148-3155.

A pharmacokinetic analysis was performed on 12 adult critically ill patients receiving cefepime 1 to 4 g/day while undergoing CRRT for severe renal failure. Details of CRRT included the following: AN69HF membrane; CVVH (n = 5) or CVVHDF (n = 7) mode; replacement fluids administered post-membrane; mean UFR ranged from 9 to 23 mL/min (540 to 1380 mL/hr); mean DFR during CVVHDF mode ranged from 857 to 1020 mL/hr. Venous blood cefepime concentrations were obtained pre- and post-membrane at multiple time points. Pertinent findings included the following [mean ± SD]:

[CVVH] half-life 12.9 ± 2.6 hr; Vd 0.46 ± 0.14 L/kg; CL_{TOTAL} 0.40 ± 0.09 mL/min/kg; CL_{CRRT} 0.15 ± 0.06 mL/min/kg; [CVVHDF] half-life 8.6 ± 1.4 hr; Vd 0.34 ± 0.12 L/kg; CL_{TOTAL} 0.46 ± 0.17 mL/min/kg; CL_{CRRT} 0.25 ± 0.04 mL/min/kg. CL_{CRRT} and CL_{TOTAL} were greater with CVVHDF (P=.002), but no significant differences were noted between CVVHDF and CVVH for CL_{TOTAL}, sieving or saturation coefficients, or ultrafiltration rates. The mean cefepime sieving coefficient during CVVH was 0.86 ± 0.04, and the mean saturation coefficient during CVVHDF was 0.78 ± 0.10. The authors concluded that cefepime 2 g/day should achieve adequate serum concentrations for susceptible pathogens (MIC ≤ 8 mg/L). This paper demonstrated the significant contribution to overall cefepime clearance by CRRT.

CEFTAZIDIME

Traunmüller F, Schenk P, Mittermeyer C, et al. Clearance of ceftazidime during continuous venovenous haemofiltration in critically ill patients. J Antimicrob Chemother 2002;49:129-134.

Twelve adult intensive care patients with acute renal failure underwent CVVH using a polysulfone filter and mean UFR 47 mL/min (2820 mL/hr). Ceftazidime 2 g IV q 8 hr was administered to treat suspected or proven infections; multiple concentrations were obtained from arterial, venous and UF samples simultaneously. Ceftazidime CL_{TOTAL} was 98.7 ± 13.2 mL/min and the clearance from hemofiltration (CL_{CRRT}) was 32.1 ± 7.9 mL/min. The sieving coefficient was 0.69 ± 0.18. Average drug removal during CVVH was 75%. Calculated half-life values varied from 3 to 15 hr. The authors concluded that 2 g q 8 hr was sufficient to treat organisms with MIC < 4 mg/L, but that the dose should be increased to at least 3 g q 8 hr for organisms with higher MIC (8 mg/L).

Mariat C, Venet C, Jehl F, et al. Continuous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. Crit Care 2006;10:R26 Available at http://ccforum.com/content/10/1/R26. Accessed April 28, 2008.

A prospective pharmacokinetic evaluation was performed on 7 critically ill adults with renal failure (creatinine clearance < 10 mL/min) and suspected or proven infection. These patients underwent CVVHDF using an AN69HF membrane, BFR 150 mL/min, DFR 1000 mL/hr, and UFR 1500 mL/hr. Replacement fluids were administered at a rate sufficient to allow 100-150 mL/min net UF. Ceftazidime was administered as a 2-g loading dose followed by 3 g per 24 hr continuous infusion. Multiple simultaneous blood and UF/dialysate samples were obtained to determine ceftazidime concentrations. Pertinent findings included: mean half-life 4 ± 1 h; Vd 19 ± 6 L; CL_{TOTAL} 62 ± 5 mL/min; CL_{CRRT} 33.6 ± 4 mL/min; sieving coefficient 0.81 ± 0.11. The half-life in these patients was comparable to critically ill patients with normal renal function, attesting to the extensive drug removal by CVVHDF. The loading dose with continuous infusion dosing regimen achieved and maintained serum concentrations in the target range of 30 to 40 mg/L, providing concentrations above 4 times the MIC for usual pathogens.

Isla A, Gascón AR, Maynar J, et al. *In vitro* AN69 and polysulphone membrane permeability to ceftazidime and *in vivo* pharmacokinetics during continuous renal replacement therapies. Chemotherapy 2007;53:194-201.

This study analyzed both *in vitro* and *in vivo* pharmacokinetics of ceftazidime during CRRT. The *in vitro* portion of this study examined ceftazidime's permeability to 2 membranes (AN69 and polysulfone); ceftazidime was infused at 150 mL/min during CVVH mode with UFR 1500 mL/hr and during CVVHD mode with DFR 1500 mL/hr. Prefilter and UF ceftazidime concentrations were obtained. In both modes, replacement fluids were administered prefilter. The authors found that the sieving coefficient (CVVH mode) and saturation coefficient (CVVHD mode) were both 1; there was no difference between the 2 membranes.

The *in vivo* portion studied 4 critically ill adults receiving ceftazidime. The dosing regimen in anuric patients was 1 g IV q 6 hr; those with creatinine clearance of at least 70 mL/min received 2 g IV q 6 hr. CRRT modes were CVVH (n = 2) and CVVHDF (n = 2). For all

patients, the UFR was 1000 mL/hr and replacement fluids were administered prefilter. The 2 patients receiving CVVHDF had DFR of 500 to 1000 mL/hr. Pertinent findings included the following [mean ± SD]: in the anuric patients, CL_{TOTAL} was 53.8 ± 25.9 mL/min and CL_{CRRT} was 28.9 ± 7.8 mL/min; in the nonanuric patients, CL_{TOTAL} was 244.1 ± 126.9 mL/min and CL_{CRRT} was 17.1 ± 0.4 mL/min; sieving/ saturation coefficient was 0.93 ± 0.06; fraction unbound was 0.86 ± 0.08; elimination half-life was 6.4 ± 2.7 hr; Vd 0.67 ± 0.31 L/kg.

Matzke GR, Frye RF, Joy MS, et al. Determinants of ceftazidime clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. Antimicrob Agents Chemother 2000;44:1639-1644.

Ceftazidime clearance by CVVH and CVVHD was studied in 8 stable, noninfected adults with end stage renal disease. Three hemofilters were evaluated (AN69, polymethylmethacrylate, and polysulfone). The patients received 1 g of ceftazidime and then underwent a 12-hour CRRT session. The authors adjusted the DFR, UFR, and BFR independently in a controlled setting to independently evaluate the impact on drug removal. Pertinent findings included the following: ceftazidime clearance in CVVH mode was dependent on UFR (higher UFR [1000 mL/hr] produced significantly higher drug removal than the lower UFR [500 mL/hr], P = .0001); no clinically significant differences were found among the 3 hemofilters; CVVHD mode removed more drug than CVVH mode; CVVHD clearance was dependent on DFR and the patient's residual renal function. The authors included dosing recommendation tables considering the CRRT mode, residual renal function, UFR and DFR. The highest dose recommended was 1 g q 12 hr (for patients undergoing CVVHD with residual creatinine clearance of 20 mL/min, DFR of 2000 mL/h and UFR of 2000 mL/hr).

CIPROFLOXACIN

Wallis SC, Mullany DV, Lipman J, et al. Pharmacokinetics of ciprofloxacin in ICU patients on continuous veno-venous haemodiafiltration. Intensive Care Med 2001;27:665-672.

Six critically ill adults receiving ciprofloxacin to treat a suspected or proven infection were studied. All patients had acute renal failure requiring CVVHDF. CRRT settings were as follows: DFR 1000 mL/h; predilution filtration solution 2000 mL/hr; dialysis effluent 3000 mL/hr; BFR 200 mL/min; AN69HF filter. The patients received ciprofloxacin 200 mg IV q 8 hr. Multiple blood and dialysate effluent samples were analyzed for ciprofloxacin concentrations. Pertinent findings included the following: CL_{CRRT} 37 ± 7 mL/min; CL_{TOTAL} 203 ± 72 mL/min; sieving coefficient 0.70 ± 0.13. The authors noted high day-to-day variation in total ciprofloxacin clearance (coefficient of variation was 36%) due to the patients themselves more so than the filter, whose coefficient of variation was only 20%. The ciprofloxacin regimen in this study was deemed appropriate to treat infections with organisms having MIC up to 0.4 mg/L, and perhaps up to 4 mg/L; however, the large intrapatient pharmacokinetic variation should be considered when designing and monitoring dosage regimens.

ENOXAPARIN

Isla A, Gascón AR, Maynar J, et al. *In vitro* and *in vivo* evaluation of enoxaparin removal by continuous renal replacement therapies with acrylonitrile and polysulfone membranes. Clin Ther 2005;27:1444-1451.

This study analyzed both *in vitro* and *in vivo* enoxaparin clearance during CRRT. The *in vitro* portion of this study examined enoxaparin permeability to 2 membranes (AN69 and polysulfone); enoxaparin was added to obtain an anti-factor Xa activity of 1 IU/mL. Two CRRT modes were tested: CVVH mode with UFR 1500 mL/hr and CVVHD mode with DFR 1500 mL/hr. In both modes, replacement fluids were administered prefilter. In both CVVH and CVVHD, enoxaparin was more permeable to the AN69 membrane than the polysulfone membrane in plasma (P < .001). The sieving coefficient in CVVH mode was 0.34 ± 0.04 [mean ± SD], for the AN69 filter compared to 0.21 ± 0.03 for the polysulfone filter. In CVVHD mode, the saturation coefficient was 0.38 ± 0.04 for the AN69 filter compared to 0.16 ± 0.03 for the

polysulfone filter.

The *in vivo* portion studied 8 critically ill adults receiving enoxaparin 0.5 to 1.09 mg/kg daily subcutaneously for the treatment or prophylaxis of venous thromboembolism. The patients' measured creatinine clearance values ranged from 0 to 36 mL/min. CRRT was provided as follows: BFR 150 to 200 mL/min; UFR 1500 to 2000 mL/hr; DFR (in CVVHDF mode) 1000 mL/hr. The sieving/ saturation coefficients in these patients were higher than the *in vitro* study [mean ± SD]: for the AN69 membrane was 0.49 ± 0.19 and 0.46 ± 0.12 for the polysulfone membrane. Additionally, the sieving/ saturation coefficients were not different between the anuric (CrCl ≤ 10 mL/min) and nonanuric (CrCl > 10 mL/min) patients. Anti-factor Xa activity levels were measured in plasma at 11 to 14 h after a dose; the range was 0.54 to 1.31 IU/mL. Two patients had supratherapeutic anti-factor Xa activity levels (> 1 IU/mL). This study highlights the fact that enoxaparin does appear to be removed to some degree by CRRT modalities; the degree to which dosing regimens should be modified is unclear. Following anti-factor Xa activity levels in these patients is advised.

FLUCONAZOLE

Yagasaki K, Gando S, Matsuda N, et al. Pharmacokinetics and the most suitable dosing regimen of fluconazole in critically ill patients receiving continuous hemodiafiltration. Intensive Care Med 2003;29:1844-1848.

A pharmacokinetic and dose-finding study was carried out in 4 critically ill adults with acute renal failure undergoing CVVHDF. All patients had *Candida* infections and were receiving fluconazole. The patients' creatinine clearance values ranged from 0.3 to 11.1 mL/min; CVVHDF was performed with a cellulose triacetate hollow fiber dialyzer 1.5 m^2. The CVVHDF settings (DFR, UFR) were unclear. Pertinent findings from the fluconazole 400 mg IV q 12 hr regimen [all values are mean (SEM)]: Cmin 6.8 (2.0) μg/mL; half-life 8.08 (0.83) hr; CL_{TOTAL} 1.14 (0.44) mL/kg/min; Vd 0.55 (0.23) L/kg. Fluconazole 800 mg IV q 24 hr produced the following: Cmin 4.2 (0.8) μg/mL; half-life 9.12 (0.75) hr; CL_{TOTAL} 0.98 (0.20) mL/kg/min; Vd 0.71 (0.16) L/kg. The authors aimed to produce trough serum concentrations (Cmin) of 10 μg/mL, which no patient achieved. However, using pharmacokinetic simulation models to calculate the dosing regimen that would achieve the target concentration, the authors recommended fluconazole 500 to 600 mg IV q 12 hr in critically ill adults undergoing CVVHDF.

Muhl E, Martens T, Iven H, et al. Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol 2000;56:671-678.

A pharmacokinetic study was undertaken to assess the impact of CVVH and CVVHD on fluconazole. Six critically ill adults with acute renal failure and life-threatening *Candida* infections received fluconazole 400 to 800 mg once daily. All patients required catecholamine infusions. Patients received CVVHD on the first day then CVVH on the second day; CRRT was performed with an AN69HF filter, BFR 90 mL/min, replacement fluids 1000 mL/hr (predilution), DFR 1000 mL/hr (during CVVHD). Mean UFR was 1158 ± 90.5 mL/hr during CVVHD and 1167 ± 81.6 mL/hr during CVVH. Multiple serum and UF/dialysate fluconazole concentrations were obtained. Pertinent findings included the following: Cmin during CVVHD was lower than during CVVH ($P \leq .05$). The Cmin range during CVVHD was 3.8 to 11.2 μg/mL compared to 6.2 to 11.9 μg/mL during CVVH. The CL_{CRRT} during CVVHD was 30.5 ± 6.0 mL/min and during CVVH was 17.5 ± 4.0 mL/min. The CL_{TOTAL} during CVVHD was 37.9 ± 4.4 mL/min and during CVVH was 25.3 ± 6.5 mL/min. Fluconazole half-life during CVVHD was 23.8 ± 6.4 hr, but it was 37.7 ± 9.3 hr during CVVH. The sieving/ saturation coefficients were 0.88 (range 0.54 to 1) during CVVHD and 0.96 (range 0.56 to 1.02) during CVVH. The Vd ranged from 0.65 to 1.3 L/kg in CVVHD mode and 0.74 to 1.24 L/kg in CVVH mode. The total clearance of fluconazole during CVVHD was almost double that of patients with normal renal function, whereas CVVH clearance approximated normal renal function. Based on the authors' calculations, adults undergoing CRRT at similar settings

to this study should receive fluconazole 1000 mg daily.

FOSFOMYCIN

Gattringer R, Meyer B, Heinz G, et al. Single-dose pharmacokinetics of fosfomycin during continuous venovenous haemofiltration. J Antimicrob Chemother 2006;58:367-371.

Twelve anuric critically ill adults with APACHE scores from 30 to 43 and mean ± SD serum creatinine 3.0 ± 1.1 mg/dL prior to CVVH received one IV 8-g dose of fosfomycin and then underwent pharmacokinetic analysis. CVVH settings were as follows: polyethylene sulfone hemofilter; BFR 180 mL/min; UFR 1500 mL/hr; replacement fluids post-dilution. Pertinent findings included the following [all data are mean ± SD]: peak serum concentration 442.7 ± 124 mg/L; trough serum concentration at 12 hr was 103.1 ± 36.6 mg/L; sieving coefficient 0.7 ± 0.1; CL_{CRRT} 1.1 ± 0.2 L/h; CL_{TOTAL} 6.4 ± 7.6 L/hr; Vd 33.7 ± 12.7 L. The authors recommend fosfomycin 8 g q 12 hr to treat susceptible organisms with MIC up to 64 mg/L; however, it should be noted that this was a single-dose study and drug accumulation was not measured.

GLUTAMINE

Berg A, Norberg Å, Martling C, et al. Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy. Intensive Care Med 2007;33:660-666.

A pharmacokinetic study was performed to ascertain glutamine loss during CRRT in critically ill patients. Twelve adults with multiple organ failure requiring CVVH (n = 2) or CVVHDF (n = 10) underwent a randomized crossover study to receive IV glutamine then placebo or placebo then glutamine on two consecutive days. The glutamine dose and formulation was 0.5 g/kg of 20% l-alanyl-l-glutamine, which corresponded to 0.32 g/kg glutamine, and was infused over 20 hr. The CRRT settings were modified as deemed clinically appropriate, and were not significantly different between groups. Intravenous glutamine resulted in higher serum glutamine concentrations compared to placebo (831 ± 367 vs. 570 ± 252 μmol/L, P < .001). Glutamine loss into ultrafiltrate or dialysate was 0.5 to 6.8 g per 24 hr. Factors relating to this loss were plasma glutamine concentration, and, more significantly, CRRT flow rate; high flow rates increased the amount of glutamine loss regardless of IV supplementation. The patients receiving IV glutamine were able to retain the extra glutamine to meet metabolic needs during CRRT.

IMIPENEM AND CILASTATIN

Fish DN, Teitelbaum I, Abraham E. Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother 2005;49:2421-2428.

The pharmacokinetics and pharmacodynamics of imipenem were studied in 12 critically ill adults receiving imipenem 0.5 g IV every 8 to 12 hr as part of their medical care. All patients had severe renal failure. Six patients underwent CVVH and 6 CVVHDF. CRRT settings were as follows: AN69HF membrane; replacement fluids delivered postmembrane; BFR 150 to 200 mL/min; DFR (in CVVHDF mode) approximately 1000 mL/hr; UFR approximately 800 to 1400 mL/hr. Pertinent findings included the following [all data are mean ± SD]: Cmin 1.4 ± 1.0 μg/mL in CVVH mode and 1.1 ± 1.1 μg/mL in CVVHDF mode (P=0.916); CL_{CRRT} 36 ± 13 mL/min in CVVH mode and 57 ± 28 mL/min in CVVHDF mode (P=0.109); CL_{TOTAL} 145 ± 18 mL/min in CVVH mode and 178 ± 18 mL/min in CVVHDF mode (P=0.01); Vd 0.36 ± 0.1 L/kg in CVVH mode and 0.37 ± 0.13 L/kg in CVVHDF mode; sieving coefficient in CVVH mode 1.21 ± 0.11 and saturation coefficient in CVVHDF mode 1.28 ± 0.17 (P = 0.417). These results show that imipenem is extensively removed during both CRRT modalities, and also that nonrenal clearance accounts for a large portion of the total elimination in patients with renal failure (70% of total clearance compared to 25% to 45% in healthy volunteers). To achieve a pharmacodynamic target of T > MIC for at least 40% of the dosing interval for organisms with MIC ≤ 4 μg/mL, the authors recommend imipenem 2 g per day in divided doses for critically ill adults receiving CRRT.

LEVOFLOXACIN

Hansen E, Bucher M, Jakob W, et al. Pharmacokinetics of levofloxacin during continuous veno-venous hemofiltration. Intensive Care Med 2001;27:371-375.

A pharmacokinetic analysis was performed on 6 critically ill adults with multiple organ failure receiving CRRT for acute renal failure. CRRT settings were as follows: AN69 hemofilter; nominal blood flow 150 mL/min; replacements fluids postdilution. All patients received levofloxacin IV 500 mg on day 1 then 250 mg daily. Pertinent findings included the following: mean peak serum concentration (on day 1) 6.4 mg/L then 8.2 mg/L after multiple doses; half-life 28 h on day 1 and 22 h after multiple doses; Vd (after the 500 mg dose) 1.24 ± 0.37 L/kg and (after multiple 250 mg doses) 0.91 ± 0.55 L/kg; sieving coefficient 0.96; CL_{CRRT} 50% of CL_{TOTAL}. The authors recommend no dosing adjustment for levofloxacin in patients with renal failure undergoing CVVH.

Guenter SG, Iven H, Boos C, et al. Pharmacokinetics of levofloxacin during continuous venovenous hemodiafiltration and continuous venovenous hemofiltration in critically ill patients. Pharmacotherapy 2002;22:175-183.

Six adult critically ill patients underwent pharmacokinetic analysis of levofloxacin during CRRT. All patients had acute renal failure (CrCl < 10 mL/min) and were receiving IV levofloxacin to treat active infections. Levofloxacin therapy had begun at least 2 days before the study period; five patients received 500 mg daily and one patient received a 500-mg loading dose followed by 125 mg daily. CRRT settings were as follows: BFR 90 mL/min; acrylonitrile AN69 filter; replacement fluids delivered predilution at 1000 mL/hr; DFR 1000 mL/hr (during CVVHDF mode, which was only used on day 1); UFR approximately 1200 mL/hr in both CVVHDF and CVVH modes. Pertinent findings included the following [all data are mean ± SD]: half-life 28.8 ± 4.5 hr in CVVHDF mode and 45.9 ± 17.7 hr in CVVH mode ($P < .05$); AUC_{24} 153.6 ± 61.5 mg·h/L in CVVHDF mode and 170.3 ± 71.4 mg·h/L in CVVH mode; CL_{CRRT} 26.05 ± 4.66 mL/min in CVVHDF mode and 15.71 ± 2.73 mL/min in CVVH mode ($P < .05$); CL_{TOTAL} 54.04 ± 23.15 mL/min in CVVHDF mode and 47.94 ± 20.03 mL/min in CVVH mode; saturation coefficient in CVVHDF mode 0.73 ± 0.14 and sieving coefficient in CVVH mode 0.79 ± 0.14; Vd in CVVHDF mode 1.51 ± 0.52 L/kg and 1.42 ± 0.42 L/kg in CVVH mode. The very small number of patients in this study and wide interpatient variability prevent generalizable dosing recommendations.

Choi G, Gomersall CD, Lipman J, et al. The effect of adsorption, filter material and point of dilution on antibiotic elimination by haemofiltration: an *in vitro* study of levofloxacin. Int J Antimicrob Agents 2004;24:468-472.

An *in vitro* study was carried out to elucidate the impact of adsorption, different filter membranes and different dilution methods on levofloxacin pharmacokinetics during CVVH. Two membranes were studied: 0.6 m^2 polyamide (Haemofilter 6S, Hospal, Lyon, France) and 0.6 m^2 polyacrylonitrile (Multiflow 60, Hospal, Lyon, France). Additionally, adsorption to the circuit was studied. The *in vitro* model of CVVH was established with a BFR of 200 mL/min and UFR 1000 mL/hr; levofloxacin 100 mg was infused and drug adsorption was measured. In the second portion of this study, replacement fluids were infused at 1000 mL/hr alternating the point at which fluids were infused into the circuit between predilution (prefilter) and postdilution (postfilter) methods. Multiple samples were collected for levofloxacin concentration determinations. Pertinent results included the following: sieving coefficient was approximately 0.9 for both filter types; point of dilution had no clinically significant impact on clearance; levofloxacin was significantly adsorbed by the polyacrylonitrile filter. The lack of adsorption data for most drugs and the resulting clinical impact represents an important area for future study.

LINEZOLID

Kraft MD, Pasko DA, DePestel DD, et al. Linezolid clearance during continuous venovenous hemodiafiltration: a case report. Pharmacotherapy 2003;23:1071-1075.

A pharmacokinetic analysis was performed to determine linezolid clearance during CV-

VHDF in a critically ill adult with acute renal and active infection. The patient had been receiving linezolid 600 mg IV q 12 hr for 14 days prior to starting CVVHDF; serum and dialysate/UF linezolid concentrations were obtained to quantify linezolid removal by CVVHDF. The CVVHDF settings were as follows: polysulfone 1.6 m^2 filter; BFR 200 mL/min; DFR 2000 mL/hr; mean UFR 774 mL/hr. Pertinent findings were the following: CL_{TOTAL} 84.7 mL/min; half-life 7.5 hr; saturation coefficient 0.77 to 0.81; CL_{CRRT} 36.5 mL/min; Vd 49 L (total weight 100 kg, dry weight approximately 80 kg). The authors concluded that CVVHDF does not significantly remove linezolid and a dosing increase is not necessary.

Meyer B, Kornek GV, Nikfardjam M, et al. Multiple-dose pharmacokinetics of linezolid during continuous venovenous haemofiltration. J Antimicrob Chemother 2005;56:172-179.

A prospective, open-label, two-phase study was conducted in 20 adult critically ill patients with anuria and suspected or proven Gram-positive infection. All patients received linezolid 600 mg IV q 12 hr. CVVH settings were as follows: polysulphone hemofilters (1.2 m^2 or 0.9 m^2 based on availability); BFR 180 mL/min; replacement fluid postdilution; mean UFR 2400 mL/hr. Pharmacokinetic analysis was designed to be performed at 12 hr and again at 72 hr. However, only 8 of 20 patients completed the designed study length of 72 hr; 19 patients had pharmacokinetic assessment performed at 12.5 hr and 8 patients at 72.5 hr. Pertinent results include the following [all data are mean ± SD]: Cmin 12 h after the beginning of the first infusion 1.9 ± 1.7 mg/L; half-life 4.3 ± 1.7 hr; AUC 79.4 ± 47.9 mg·h/L; CL_{TOTAL} 9.3 ± 3.5 L/hr; CL_{CRRT} 1.9 ± 0.8 L/hr; sieving coefficient 0.72 ± 0.12; Vd 51 ± 12 L. This dosing regimen achieved 57% ± 32% time above MIC (4 mg/L) and 93% ± 44% time above MIC (2 mg/L). The authors conclude that linezolid is extensively removed by CVVH; clearance is similar to or higher than patients with normal renal function. A dosing regimen of 600 mg at least twice daily is recommended for critically ill adults undergoing CVVH.

Fiaccadori E, Maggiore U, Rotelli C, et al. Removal of linezolid by conventional intermittent hemodialysis, sustained low-efficiency dialysis, or continuous venovenous hemofiltration in patients with acute renal failure. Crit Care Med 2004;32:2437-2442.

Linezolid pharmacokinetics during an intermittent CVVH session were studied in 2 adult patients with oliguric renal failure. One dose of linezolid 600 mg IV was administered then CVVH was performed using AN69XT 1.65 m^2 membranes, replacement fluids administered predilution at 35 mL/kg/hr, and BFR 150 mL/min. The CVVH session lasted 10.5 and 12 hr in the 2 patients. Pertinent results were as follows: sieving coefficient 0.54 to 0.67 (4 measurements); half-life 2.6 hr and 6.5 hr in each patient, respectively; CL_{CRRT} 19 to 21 mL/min; Vd 0.4 to 0.5 L/kg.

Mauro LS, Peloquin CA, Schmude K, et al. Clearance of linezolid via continuous venovenous hemodiafiltration. Am J Kid Dis 2006;47:E83-E86.

A case report described the pharmacokinetics of linezolid during CVVHDF in an adult critically ill patient with renal failure and sepsis. Linezolid 600 mg IV q 12 hr was initiated to treat vancomycin-resistant *Enterococcus faecium* from the patient's urine. The pharmacokinetic analysis was performed on day 4 of treatment. CVVHDF settings were as follows: polyacrylonitrile filter 1 m^2; DFR 1200 mL/hr; BFR 200 mL/min; replacement fluids infused prefilter at 200 mL/hr; combined dialysate and UF outflow 1025 to 1800 mL/hr. Pertinent results included the following: linezolid serum trough concentration 0.3 mg/L; AUC 52.9 mg·h/L; CL_{TOTAL} 189 mL/min (1.53 mL/min/kg); CL_{CRRT} 15.8 to 21.6 mL/min. The authors concluded that CVVHDF contributed only a small amount to overall linezolid clearance in this patient, and that supplemental doses were not required.

LORAZEPAM

Swart EL, de Jongh J, Zuideveld KP, et al. Population pharmacokinetics of lorazepam and midazolam and their metabolites in intensive care patients on continuous

venovenous hemofiltration. Am J Kid Dis 2005;45:360-371.

The pharmacokinetics of midazolam, lorazepam, and metabolites were assessed in 20 critically ill adults with renal failure receiving CVVH. Patients received continuous infusion midazolam (n = 10) or lorazepam (n = 10) titrated to provide adequate sedation. The CVVH settings were as follows: BFR 180 mL/min; replacement fluids at 2000 mL/hr either predilution or postdilution. The authors concluded that midazolam and lorazepam are not effectively removed by CVVH; however, the glucuronide metabolites (lorazepamglucuronide and 1-hydroxy-midazolamglucuronide) are significantly eliminated.

MEROPENEM

Isla A, Maynar J, Sanchez-Izquierdo JA, et al. Meropenem and continuous renal replacement therapy: *in vitro* permeability of 2 continuous renal replacement therapy membranes and influence of patient renal function on the pharmacokinetics in critically ill patients. J Clin Pharmacol 2005;45:1294-1304.

This study analyzed both *in vitro* and *in vivo* pharmacokinetics of meropenem during CRRT. The *in vitro* portion of this study examined permeability to 2 membranes (AN69 and polysulfone); meropenem was infused at a constant rate during CVVH mode with UFR 1500 mL/hr and during CVVHD mode with DFR 1500 mL/hr. In both modes, replacement fluids were administered prefilter. The authors found that the sieving coefficient (CVVH mode) and saturation coefficient (CVVHD mode) were both approximately 1; there was no difference between the 2 membranes.

The *in vivo* portion studied 20 adults with varying degrees of renal dysfunction receiving meropenem. Patients in group I (n = 7, CrCl < 5 mL/min) received meropenem 500 mg IV q 6 to 8 hr (1 patient received 100 mg q 8 hr); group II (n = 7, CrCl 10-45 mL/min) received 500 mg q 6 hr (1 patient received 1000 mg q 8 hr); group III (n = 6, CrCl > 50 mL/min) received 2000 mg q 8 hr (1 patient received 1000 mg q 6 hr). CRRT modes were CVVH (n = 10) and CVVHDF (n = 10).The UFR was 800 to 2500 mL/hr and replacement fluids were administered prefilter; BFR was 100 to 220 mL/min. The 10 patients receiving CVVHDF had DFR of 500 or 1000 mL/hr. Pertinent findings included the following: the mean sieving/saturation coefficient was 0.8; group I patients had half-life 3.7 ± 0.8 hr, CL_{CRRT} 27 ± 7 mL/min, CL_{TOTAL} 150 ± 76 mL/min, and Vd 0.57 ± 0.29 L/kg; group II patients had half-life 2.7 ± 0.7 hr, CL_{CRRT} 32 ± 7 mL/min, CL_{TOTAL} 134 ± 57 mL/min, and Vd 0.37 ± 0.10 L/kg; group III patients had half-life 1.5 ± 0.5 hr, CL_{CRRT} 16 ± 7 mL/min, CL_{TOTAL} 1065 ± 662 mL/min, and Vd 1.31 ± 0.90 L/kg. In groups I and II, but not group III, the mean Cmin was above 4 mg/L. CRRT contributed significantly to meropenem clearance in patients with moderate to severe renal failure. In patients with mild renal dysfunction, CRRT did not play as big a role in overall clearance; however, it did result in potentially subtherapeutic serum concentrations, highlighting the importance of aggressive dosing and monitoring.

Isla A, Rodriguez-Gascón A, Trocóniz IF, et al. Population pharmacokinetics of meropenem in critically ill patients undergoing continuous renal replacement therapy. Clin Pharmacokinet 2008;47:173-180.

A pharmacokinetic analysis of 20 critically ill adults undergoing CRRT receiving meropenem was used to create a population pharmacokinetic model. CRRT modes were CVVH (n = 10) and CVVHDF (n = 10).The UFR was 800 to 2500 mL/hr and replacement fluids were administered prefilter; BFR was 100 to 220 mL/min. The 10 patients receiving CVVHDF had DFR of 500 or 1000 mL/hr. The resulting population pharmacokinetic model was validated. Significant covariates included CrCl and whether the patient was septic or polytraumatized. The authors concluded that the model was useful in determining continuous infusion meropenem regimens for patients undergoing CRRT.

Ververs TF, van Dijk A, Vinks SA, et al. Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. Crit Care Med 2000;28:3412-3416.

Five critically ill adults with renal failure requiring CVVH underwent pharmacokinetic analysis. All patients received meropenem 500

mg IV q 12 hr to treat life threatening infections. CVVH settings were as follows: BFR 200 mL/min; polyacrylonitrile filter; UFR 1500 to 1800 mL/hr; replacement fluids administered at 1500 mL/hr postdilution. Pertinent findings included the following [mean ± SD]: Cmin 3.0 ± 0.9 mg/L; half-life 6.4 ± 2 hr; AUC 130 ± 26 mg·h/L; CL_{TOTAL} 4.6 ± 0.9 L/hr; CL_{CRRT} 1.0 ± 0.4 L/hr; Vd 0.37 ± 0.15 L/kg. The authors concluded that meropenem 500 mg q 12 hr was sufficient. It is noteworthy that this dosing regimen is considerably lower than more recent recommendations; however, the pharmacodynamic target(s) and CRRT settings vary among institutions.

Valtonen M, Tiula E, Backman JT, et al. Elimination of meropenem during continuous veno-venous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother 2000;45:701-704.

The elimination characteristics of 3 different CRRT settings were studied in 6 adult patients with renal failure receiving meropenem. Separate pharmacokinetic analyses were performed during 3 consecutive 12-hour time periods: first, during CVVH; second, during CVVHDF with DFR 1000 mL/hr; and third, during CVVHDF with DFR 2000 mL/hr (a polysulfone filter was used in all patients). The BFR was 100 mL/min and the UFR was 400 mL/hr (these are decreased compared to many other studies). A dose of meropenem was infused prior to each of the 3 study periods. Pertinent findings included the following [data are mean ± SD during the 3 consecutive study periods, as above]: half-life 7.5 ± 2.0 hr, 5.6 ± 1.4 hr, 4.8 ± 1.2 hr; CL_{TOTAL} 3.3 ± 2.3 L/hr, 4.7 ± 2.7 L/hr, 5.7 ± 3.6 L/hr. Significant differences ($P<0.5$) were found in half-life between CVVHDF and CVVH periods and between the 2 CVVHDF periods, and in clearance between the CVVHDF and CVVH periods. This data may be useful in assisting practitioners design dosing regimens when using similar CRRT settings to this study.

Langgartner J, Vasold A, Glück T, et al. Pharmacokinetics of meropenem during intermittent and continuous intravenous application in patients treated by continuous renal replacement therapy. Intensive Care Med 2008; Epub ahead of print;DOI 10.1007/s00134-008-1037-7.

A randomized, prospective, crossover study analyzed the differences in meropenem pharmacokinetics between continuous infusion and intermittent doses in 6 adults with renal failure receiving CRRT. Patients were randomized to receive meropenem 500 mg IV followed by 2000 mg per 24 hr continuous infusion for 2 days then cross over to receive 1000 mg IV q 12 hr for 2 days, or to start with intermittent dosing followed by the continuous infusion. Analysis was performed on days 2 and 4. CVVHD settings were as follows: polysulfone filter 1.4 m^2; BFR 150 mL/min; UFR 25 mL/kg/hr. Pertinent findings were as follows [data are medians with 25% and 75% interquartile range]: [intermittent dosing] Cmin 8.2 (5.4, 10.1) mg/L; half-life 5.3 (5.1, 7.0) hr; CL_{TOTAL} 4.32 (3.93, 4.96) L/hr; 68% time > MIC 4 mg/L; 46% time > MIC 8 mg/L; Vd 32.3 (28.9, 40.7) L; [continuous infusion] Cmin 15.7 (12.6, 18.5) mg/L; CL_{TOTAL} 4.40 (3.58, 5.58) L/h; 100% time > MIC 4 mg/L and MIC > 8 mg/L.

Robatel C, Decosterd LA, Biollaz J, et al. Pharmacokinetics and dosage adaptation of meropenem during continuous venovenous hemodiafiltration in critically ill patients. J Clin Pharmacol 2003;43:1329-1340.

Meropenem pharmacokinetics were studied in 15 adult intensive care patients with renal failure receiving CVVHDF. Dosing ranged from 500 to 1000 mg IV q 8 to 12 hr. CVVHD settings were as follows: polyacrylonitrile AN69HF 0.9 m^2 filter; BFR 90 to 150 mL/min; replacement fluids (predilution) 0 to 1000 mL/hr; DFR 600 to 1500 mL/hr; net UFR 10 to 270 mL/hr. Pertinent results included the following [data are averages]: trough concentration at end of 12-hr dosing interval 4.1 mg/L (500 mg dose) and 7.6 mg/L (1000 mg dose); half-life 5.1 hr; CL_{TOTAL} 4.5 L/hr; CL_{CRRT} 1.6 L/hr; sieving coefficient 0.65; Vd 33 L. The authors utilized pharmacokinetic simulation models to make dosing recommendations, predicting that meropenem 750 mg q 8 hr or 1500 mg q 12 hr, assuming similar patients and CVVHDF settings, should produce trough concentrations above an MIC of 4 mg/L for more than 75% of the dosing interval.

Kuti JL, Nicolau DP. Derivation of meropenem dosage in patients receiving continuous veno-venous hemofiltration based on pharmacodynamic target attainment. Chemotherapy 2005;51:211-216.

This study took pharmacokinetic data reported from 4 published studies of meropenem in similar CVVH settings and used pharmacodynamic modeling to determine dosing that will achieve optimal bactericidal exposure against *Pseudomonas aeruginosa* and *Acinetobacter* species. Monte Carlo simulation using the pharmacokinetic data on CVVH from the literature combined with national susceptibility data (from the year 2003, MIC breakpoint 4 mg/L) predicted that meropenem 1000 mg q 8 hr or 500 mg q 6 hr had the highest likelihood of attaining bactericidal exposure (defined as free drug concentrations above the MIC for 40% of the dosing interval).

Krueger WA, Neeser G, Schuster H, et al. Correlation of meropenem plasma levels with pharmacodynamic requirements in critically ill patients receiving continuous veno-venous hemofiltration. Chemotherapy 2003;49:280-286.

Eight critically ill adults with acute anuric or oliguric renal failure requiring CVVH underwent a pharmacokinetic study. All patients received meropenem 500 mg IV q 12 hr for 3 to 5 days before starting the analysis. CVVH settings were as follows: BFR 10 mL/min; UFR 1600 mL/hr; AN69HF hemofilter 0.9 m^2; replacement fluids administered postdilution (n=7) or predilution (n=1). Pertinent results included the following [all data are mean ± SD]: trough concentration just before and at 12 hr after a dose at steady state 2.1 ± 0.9 mg/L and 2.4 ± 1.5 mg/L, respectively; half-life 3.63 ± 0.77 hr; sieving coefficient 0.91 ± 0.10; CL_{TOTAL} 83 ± 22 mL/min; CL_{CRRT} 24 ± 8 mL/min; Vd 0.28 ± 0.07 L/kg; time above MIC (4 mg/L) 8.22 ± 2.23 hr; time above MIC (8 mg/L) 4.72 ± 1.34 hr. The pharmacodynamic target chosen for this study was time above MIC for 40% of the dosing interval, considering the post-antibiotic effect of meropenem. The authors conclude that meropenem 500 mg IV q 12 hr is appropriate to treat infections with MIC up to 4 mg/L in adults with renal failure undergoing CVVH.

MICAFUNGIN

Hirata K, Aoyama T, Matsumoto Y, et al. Pharmacokinetics of antifungal agent micafungin in critically ill patients receiving continuous hemodialysis filtration. Yakugaku Zasshi 2007;127:897-901.

These authors compared the pharmacokinetics of micafungin in adult intensive care patients: 9 patients not receiving CRRT and 4 patients who required CVVHDF for fluid and electrolyte balance. Micafungin doses ranged from 150 to 300 mg IV per day. CVVHDF settings were as follows: polymethyl methacrylate membrane; replacement fluids delivered postfilter; BFR 1 to 1.5 mL/kg/min; DFR 500 to 1000 mL/hr; UFR 800 to 1300 mL/hr. Pertinent findings included the following: [CVVHDF] extraction ratio 3.6% ± 3.9%; Vd 17.5 ± 4.4 L; CL_{TOTAL} 1.4 ± 0.7 L/hr. The Vd and clearance were not significantly different compared to patients not receiving CVVHDF. The authors concluded that CVVHDF does not significantly remove micafungin and that a dosage adjustment is not necessary.

MIDAZOLAM (SEE ALSO LORAZEPAM)

Bolon M, Bastien O, Flamens C, et al. Midazolam disposition in patients undergoing continuous venovenous hemodialysis. J Clin Pharmacol 2001;41:959-962.

Three adult intensive care patients underwent a pharmacokinetic analysis of midazolam and its metabolites' removal during CVVHD. All patients had renal failure (CrCl < 10 mL/min). Midazolam was infused at 0.1 mg/kg followed by 0.05 mg/hr [authors may have intended 0.05 mg/kg/hr] infusion. Pertinent findings included the following: midazolam CL_{CRRT} 0.13 to 4.7 mL/min, sieving coefficient 0.006 to 0.26, 0.2% removal; half-life 7.6 to 22.8 hr; Vd 1.2 to 3.2 L/kg; 1-hydroxy-midazolam CL_{CRRT} 0.14 mL/min, sieving coefficient 0.007; 1-hydroxy-midazolam glucuronide CL_{CRRT} 7.8 to 12 mL/min, sieving coefficient 0.36 to 0.63. The authors concluded that midazolam is not effectively removed by CVVHD.

MOXIFLOXACIN

Fuhrmann V, Schenk P, Jaeger W, et al. Pharmacokinetics of moxifloxacin in patients undergoing continuous venovenous haemodiafiltration. J Antimicrob Chemother 2004;54:780-784.

Nine adult critically ill patients with renal failure requiring CVVHDF underwent a pharmacokinetic study. All patients were anuric; serum creatinine [mean ± SD] was 4.3 ± 2.5 mg/dL. Moxifloxacin 400 mg IV daily was administered to treat suspected or proven infections. CVVHDF settings were as follows: AN69HF hemofilter; BFR 150 mL/min; replacements fluids administered predilution at 1000 mL/hr; DFR 1000 mL/hr; mean UFR 1000 mL/h. Pertinent results included the following: arterial Cmax after first dose 3.76 ± 2.02 mg/L; half-life 9.87 ± 3.26 hr; Vd 270 ± 133 L; AUC 24.95 ± 11.25 mgCh/L; sieving coefficient 0.84 ± 0.16; CL_{TOTAL} 19.09 ± 8.22 L/hr; CL_{CRRT} 1.63 ± 0.33 L/hr; 10% removal. The authors concluded that the pharmacokinetics of moxifloxacin in patients with renal failure undergoing CVVHDF are similar to those of healthy patients, therefore, no dosing adjustment is necessary.

MYCOPHENOLATE

Cussonneau X, Bolon-Larger M, Prunet-Spano C, et al. Evaluation of MPA and MPAG removal by continuous venovenous hemodiafiltration and continuous venovenous hemofiltration. Ther Drug Monit 2008;30:100-102.

Four adult heart transplant recipients participated in a pharmacokinetic study to assess the removal of mycophenolic acid (MPA) and its phenolic glucuronide metabolite (MPAG) during CRRT. All patients had acute renal failure; 2 required CVVH and 2 CVVHDF. Mycophenolate mofetil doses ranged from 500 to 1500 mg twice daily orally or IV. CRRT settings were as follows: BFR 120 to 250 mL/min; UFR 750 mL/hr (CVVHDF) and 45 mL/kg/hr (CVVH); DFR 1000 to 1500 mL/hr; duration of CRRT ranged from 4 to 72 hr. Pertinent findings included the following: sieving coefficient 0.02 to 0.04 (MPA) and 0.16 to 0.33 (MPAG); clearance 0.71 to 2.28 mL/min (MPA) and 7 52 to 19.45 mL/min (MPAG); clearance was not significantly different between CVVH and CVVHDF modes. The authors concluded that the highly protein bound MPA is not removed significantly by CRRT; however, in renal failure as protein binding decreases, the relative free fraction decreases. A significant portion of MPAG is removed by CRRT. Emphasis is placed on monitoring serum concentrations.

PIPERACILLIN AND TAZOBACTAM

Valtonen M, Tiula E, Takkunen O, et al. Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother 2001;48:881-885.

The elimination characteristics of 3 different CRRT settings were studied in 6 adult patients with renal failure receiving piperacillin/tazobactam. Separate pharmacokinetic analyses were performed during 3 consecutive 12-hour time periods: first, during CVVH; second, during CVVHDF with DFR 1000 mL/hr; and third, during CVVHDF with DFR 2000 mL/hr (a polysulphone filter was used in all patients). The BFR was 100 mL/min and the average UFR was 800 mL/hr. A dose of 4 g piperacillin and 0.5 g tazobactam was infused prior to each of the 3 study periods. Pertinent findings included the following [data are for piperacillin, mean ± SD during the 3 consecutive study periods, as above]: half-life 7.7 ± 2.3 hr, 6.7 ± 1.9 hr, 6.1 ± 2.0 hr; CL_{TOTAL} 3.89 ± 1.23 L/hr, 5.06 ± 1.68 L/hr, 5.48 ± 2.11 L/hr. Significant differences ($P < 0.5$) were found in half-life between CVVHDF and CVVH periods and between the 2 CVVHDF periods, and in clearance between the CVVHDF and CVVH periods. Data for tazobactam are also included in the paper. This data may be useful in assisting practitioners design dosing regimens when using similar CRRT settings to this study.

Mueller SC, Majcher-Peszynska J, Hickstein H, et al. Pharmacokinetics of piperacillin-tazobactam in anuric intensive care patients during continuous venovenous hemodialysis. Antimicrob Agents Chemother 2002;46:1557-1560.

Eight critically ill adults with acute renal failure requiring CVVHD and receiving piperacillin/tazobactam underwent a pharmacokinetic analysis. All patients had less than 100 mL urine output per day. Piperacillin/tazobactam doses ranged from 2/0.25 g to 4/0.5 g IV q 8 to 24 hr. CVVHD settings were as follows: AN69 filter; BFR 150 mL/min; DFR 1500 mL/hr; UFR 80 to 200 mL/hr. The pharmacodynamic target was to achieve time above MIC for 50% of the dosing interval; MIC breakpoints were taken from National Committee for Clinical Laboratory Standards 2000. Pertinent results included the following [data are mean ± SD (unless noted) for piperacillin, followed by tazobactam]: saturation coefficient 0.87 ± 0.21, 0.64 ± 0.19; half-life 4.3 ± 1.2 hr, 5.6 ± 1.3 hr; Vd 0.31 ± 0.07 L/kg, 0.24 ± 0.09 L/kg; CL_{TOTAL} (median, range) 47 (26-220) mL/min, 30 (22-59) mL/min; CL_{CRRT} 22 ± 5 mL/min, 17 ± 5 mL/min. The authors performed simulations of piperacillin/tazobactam regimens designed to attain the pharmacodynamic target and, therefore, recommend 4 g piperacillin/0.5 g tazobactam q 12 hr or 2 g piperacillin/0.25 g tazobactam q 8 hr in this patient population.

TACROLIMUS

Kishino S, Takekuma Y, Sugawara M, et al. Influence of continuous venovenous haemodiafiltration on the pharmacokinetics of tacrolimus in liver transplant recipients with small-for-size grafts. Clin Transplant 2003;17:412-416.

Adults receiving living donor liver transplantation with small-for-size grafts may receive CVVHD following the transplantation to serve as artificial liver support. These authors studied the impact of CVVHD on the pharmacokinetics of tacrolimus in 3 adults with small-for-size grafts. Tacrolimus was given as a continuous infusion 0.0375 or 0.025 mg/kg/day or orally 0.05 mg/kg/day divided q 12 hr. CVVHD settings were as follows: cellulose triacetate dialyzer 1.5 m^2; BFR 100 mL/min; DFR 1000 mL/hr; UFR 2000 mL/hr; replacement fluids postdilution. The authors concluded that CVVHD did not affect the serum tacrolimus concentration and that no dosage adjustment is required.

TRACE ELEMENTS

Berger MM, Shenkin A, Revelly J, et al. Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. Am J Clin Nutr 2004;80:410-416.

A prospective, randomized crossover trial was conducted on 11 critically ill adults to analyze the impact of CVVHDF on trace element balance. Two replacement solutions were used, containing either bicarbonate or lactate as the buffer, in 2 consecutive 24-hr periods. CVVHDF settings were as follows: AN69 filter; DFR 1000 mL/hr; UFR 1000 mL/hr. Patients received daily IV trace elements and multivitamins as part of the standard parenteral nutrition, plus 100 mg thiamine. Pertinent results included the following: CRRT was associated with significant trace element losses. The losses were not significantly different between the 2 replacement fluid solutions. The patients developed a positive zinc balance due to the large volume of zinc-containing replacement fluids infused. However, selenium, copper, and thiamine balances were negative despite IV supplementation.

Churchwell MD, Pasko DA, Btaiche IF, et al. Trace element removal during *in vitro* and *in vivo* continuous haemodialysis. Nephrol Dial Transplant 2007;22:2970-2977.

This study evaluated both the *in vitro* transmembrane trace element clearance by CRRT and also *in vivo* trace element removal in 10 adult critically ill patients receiving CVVHDF. The CVVHDF settings were as follows: mean DFR 2000 mL/hr; mean BFR 173 ± 25 mL/min; mean UFR 7.65 ± 3.05 mL/min; polysulfone filter. The authors found that minimal copper, manganese, selenium and zinc were removed by CVVHDF, and that standard trace element supplementation is sufficient to replace losses.

VANCOMYCIN

Shah M, Quigley R. Rapid removal of vancomycin by continuous venovenous hemofiltration. Pediatr Nephrol 2000;14:912-915.

These authors report the impact of CVVH on the pharmacokinetics of vancomycin in a 14-year-old, 39-kg girl with a coagulase-negative staphylococcus ventriculoperitoneal shunt infection. The patient had normal renal function at baseline, and received vancomycin IV 60 mg/kg/day divided q 8 hr. Eight days after admission she developed renal failure (serum creatinine 6.6 mg/dL) and vancomycin serum concentration was 250 mg/L. CVVH was started as follows: HF 700 Renaflo Hemofilter 0.71 m^2; BFR 150 mL/min; UFR 1800 mL/hr, replacement fluids delivered prefilter. Vancomycin concentrations decreased to 27 mg/L by the end of the 38 hr CVVH period. The sieving coefficient for vancomycin was 0.6. The patient's residual renal function was 15.2 mL/min/1.73 m^2. The half-life of vancomcyin in this patient was 53 hours before CVVH and 13 hr during CVVH. This paper illustrates the significant removal of vancomycin by CVVH.

DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. Br J Clin Pharmacol 2004;58:259-268.

Vancomycin pharmacokinetics were analyzed in 10 critically ill adults receiving 750 mg IV q 12 hr while undergoing CVVHDF for acute renal failure. CVVHDF settings were as follows: AN69HF filter; BFR 200 mL/min; DFR 1000 mL/hr; predilution fluids 2000 mL/hr; total effluent 3000 mL/hr. Pertinent results include the following [mean ± SD]: sieving coefficient 0.7 ± 0.1; half-life 15.6 ± 8.7 hr; CL_{TOTAL} 2.5 ± 0.7 L/hr; CL_{CRRT} 1.8 ± 0.4 L/hr; Vd 49.7 ± 29.1 L; trough concentration after first vancomycin dose 9.4 ± 2.8 mg/L; subsequent trough concentrations 19.2 ± 5.2 mg/L. The authors conclude that this dosing regimen achieves adequate serum trough concentrations to attain the pharmacodynamic target (5 to 15 mg/L); however, accumulation occurs after multiple doses, warranting serum concentration monitoring and dosing adjustment if needed.

Tian Q, Gomersall CD, Leung PP, et al. The adsorption of vancomycin by polyacrylonitrile, polyamide, and polysulfone hemofilters. Artif Organs 2008;32:81-84.

An *in vitro* analysis was performed to determine the degree and reversibility of adsorption of vancomycin to 3 different CRRT filter types. The filters studied were: 0.6 m^2 polyacrylonitrile (AN69, Multiflow 60, Hospal, Meyzieu, France), 0.6 m^2 polyamide (Hemofilter 6S, Gambro, Hechingen, Germany), and 0.7 m^2 polysulfone (Ultraflux AV400S, Fresenius, Bad Homburg, Germany). The CVVH circuit was set as follows: pH 7.40; BFR 200 mL/min; UFR 1000 mL/hr. Pertinent results included the following: vancomycin adsorption occurred rapidly and was complete within 30 minutes; decreasing the vancomycin concentration did not affect adsorption; polyacrylonitrile filters adsorbed significantly more vancomycin than the polyamide or polysulfone filters. The amount of vancomycin adsorbed when the concentration was 40-45 mg/L with normal pH was 5 to 10 mg, which is probably clinically irrelevant.

VORICONAZOLE

Robatel C, Rusca M, Padoin C, et al. Disposition of voriconazole during continuous veno-venous haemodiafiltration (CVVHDF) in a single patient. J Antimicrob Chemother 2004;54:269-270.

A case report described the impact of CVVHDF on voriconazole pharmacokinetics in an adult critically ill patient with renal failure. Voriconazole was administered IV at 6 mg/kg twice, 14 hours apart, then 4 mg/kg q 12 hr. CVVHDF settings were as follows: AN69 filter 0.9 m^2; BFR 120 mL/min; DFR 1000 mL/hr; predilution fluids 500 mL/hr; UFR 220 mL/hr. Voriconazole pharmacokinetic analysis was performed at the time of the second 6 mg/kg dose. Pertinent findings were as follows: half-life 13.7 hr; sieving coefficient 0.53; Vd 399 L; AUC 16.6 mgChr/L; CL_{TOTAL} 20.3 L/hr. The authors concluded that CVVHDF did not impact the clearance of voriconazole and that dosing adjustment is not necessary.

Quintard H, Papy E, Massias L, et al. The pharmacokinetic profile of voriconazole during continuous high-volume venovenous hemofiltration in a critically ill patient. Ther Drug Monit 2008;30:117-119.

These authors describe a case in which an adult critically ill patient with anuric renal

failure receiving CVVH was receiving voriconazole to treat an abdominal infection. Voriconazole was administered IV at 4 mg/kg q 12 hr; pharmacokinetic analysis occurred on day 11 of therapy. The CVVH settings were as follows: 1.9 m^2 polyethersulfone filter; BFR 200 mL/min; predilution flow 1000 mL/hr; postdilution flow 2000 mL/hr. Pertinent findings included the following: Cmax 6.8 mg/L; half-life 16.5 hr; CL_{TOTAL} 5.4 L/hr; Vd 128.6 L; sieving coefficient 0.58.

Fuhrmann V, Schenk P, Jaeger W, et al. Pharmacokinetics of voriconazole during continuous venovenous haemodiafiltration. J Antimicrob Chemother 2007;60:1085-1090.

A pharmacokinetic analysis was performed on 9 critically ill adults with acute renal failure and suspected or proven fungal infection. All patients were anuric. Voriconazole was administered at 6 mg/kg IV to all patients; 4 of the 9 patients received continued dosing with a second 6 mg/kg dose 12 hr later, followed by 4 mg/kg/dose q 12 hr. CVVHDF was carried out as follows: AN69 filter; BFR 9 L/h; predilution fluid 1000 mL/hr; DFR 1000 mL/hr. Pertinent findings were the following [mean ± SD, data following the first dose in 8 patients]: Cmax 5.9 ± 2.9 mg/L; Cmin 1.1 ± 0.3 mg/L; CL_{TOTAL} 12.9 ± 6.7 L/hr; CL_{CRRT} 1.1 ± 0.3 L/hr; sieving coefficient 0.56 ± 0.16; Vd 228 ± 42 L; half-life 14.7 ± 6.5 hr; % removal by CVVHDF 11% ± 7%. In one patient that also had cirrhosis, the pharmacokinetic parameters were different, most notably was the half-life of 52 hr. There was not significant drug accumulation after repeated doses. The authors concluded that CVVHDF does not alter the pharmacokinetics of voriconazole, and that patients in renal failure do not need dose adjustment. However, patients with cirrhosis may need decreased maintenance doses, but this population requires further study.

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