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# Pharmacokinetics of Catecholamines During Hemofiltration in Pediatric Patients

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**Background:** Continuous hemofiltration is used in pediatric patients with acute renal failure. Many of these patients are treated with catecholamines for hemodynamic instability. The authors studied the pharmacokinetics of dopamine and dobutamine on patients undergoing continuous venovenous hemofiltration.

**Methods and Results:** Three critically ill pediatric patients with acute renal failure and cardiovascular instability treated with hemofiltration and intravenous infusion of dopamine and/or dobutamine were entered into the study. Blood samples were drawn at steady-state levels from the arterial port (inflow) of the hemofilter, from the venous port (outflow) of the hemofilter, and from the ultrafilter. Sixteen (n = 16) pharmacokinetic measurements were made, six (n = 6) for dopamine and 10 (n = 10) for dobutamine. The clearance of dopamine by the hemofilter was 0.078 ± 0.011 mL/kg/min, and for dobutamine it was 0.036 ± 0.008 mL/kg/min. On the average, 0.56% of the dopamine dose and 0.13% of the dobutamine dose was removed by the hemofilter.

**Conclusions:** The pharmacokinetics of dopamine and dobutamine at the dosage range of 5–25 μg/kg/min are not altered by continuous hemofiltration. Relative to total plasma clearance, negligible amounts of the drug were removed. The dosage of these catecholamines need not be adjusted during continuous hemofiltration.

**Key words:** pharmocokinetics, catecholamines, hemofiltration, acute renal failure.

Continuous arteriovenous hemofiltration (CAVH) and continuous venovenous hemofiltration (CVVH) are currently used in the treatment of acutely ill pediatric patients with acute renal failure (1). Although it has been reported that this form of renal replacement therapy causes less hemodynamic instability than hemodialysis (2–3), patients on CVVH or CAVH frequently require the use of catecholamines for the treatment of cardiovascular instability due to multiple organ dysfunction syndrome (MODS). It is therefore important to understand the pharmacokinetics of catecholamines during hemofiltration to help physicians to make decisions regarding the dosing of these drugs. To our knowledge, this is the first study to evaluate the pharmacokinetics of dopamine (DOP) and dobutamine (DOB) in pediatric intensive care unit (PICU) patients with acute renal failure undergoing CVVH.

## Methods

The study was approved by the Committee on Clinical Investigation of Children's Hospital Los Angeles. Informed consent was obtained from each child's parents. Patients admitted to the PICU who required CVVH and intravenous DOP and/or DOB were eligible for the study. DOP and DOB infusions were ordered and adjusted by the primary physician based on the clinical condition of the patient.

The DOP and DOB solutions were prepared using 5% dextrose in water and infused intravenously with a calibrated AVI pump model 200 (AVI Inc, St. Paul, MN). The infusion rate ranged from 0.5–3.0 mL/h, which corresponded to infusions from 5.0 μg/

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kg/min–25.0 μg/kg/min. The infusions were adjusted by the primary physician according to the patient's clinical condition.

Each patient's age, sex, weight, and height were recorded. The patients were on CVVH using the Amicon Diafilter-20S Hemofilter with a pore size of 10,000 d (Amicon Ireland, Ltd, Limerick, Ireland). Blood flow through the filter was 15 mL/min–17 mL/min using the AVI pump model 200. Hemofiltration rates ranged from 10 mL/h–100 mL/h also using the AVI pump model 200.

Blood samples were collected at steady state (at least more than 4 half-lives after the start of a particular dosing rate) from the arterial sampling port of the filter tubing (outflow), the venous sampling port of the filter tubing (inflow), and the ultrafiltrate. All samples were drawn simultaneously. Samples were also obtained from the medication infusions to ensure that the correct concentration was being infused. Blood was collected in ice-cold centrifuge tubes prepared to contain 25 mg ethylene glycol tetra-acetic acid per milliliter of blood collected and 75 mg reduced glutathione per milliliter of blood collected. Blood samples were centrifuged at −5°C and 3000*g* for 5 min immediately after being collected, and the plasma was stored at −70°C until analyzed. Plasma DOP and DOB concentrations were measured using reverse-phase high-pressure liquid chromatography with electrochemical detection. Samples of DOP and DOB infusions solutions were also analyzed, and their DOP and DOB concentrations were found to differ by no more than 5% from the calculated values. The assay sensitivity was 100 pg/mL. It had a within-run coefficient of variation of less than 5% for concentrations above 10 ng/mL and less than 8% for concentrations below 10 ng/mL, and a between-run coefficient of less than 8%. The assay was linear (intercept not significantly different from 0) for plasma concentrations of 0.05 ng/mL ($r$ = .9978, 0.5 mL extracted) to 1000 ng/mL ($r$ = .9999, 0.1 mL extracted).

Pharmacokinetic calculations were done using the following formulas (4):

$$\begin{aligned} SC &= C_{ult}/C_{ss} = 2C_{ult}/(C_{art} + C_{ven}) \\ CL_{hf} &= (HFR \times SC)/Weight \\ CL_{wb} &= Dose/C_{ss} \\ EL_{hf} &= HFR \text{ x } C_{ult} \\ \%EL &= EL_{hf}/(Dose \times Weight) \\ &= CL_{hf}/CL_{wb} \end{aligned}$$

where SC is sieving coefficient, $C_{ult}$ is drug concentration in the ultrafiltrate, $C_{ss}$ is the steady-state drug concentration (prefilter), $C_{art}$ is drug concentration from the arterial port of the hemofilter (inflow), $C_{ven}$ is drug concentration from the venous side of the hemofilter (outflow), $CL_{hf}$ is drug clearance by the hemofilter, $CL_{wb}$ is total plasma clearance, $EL_{hf}$ is the amount of the drug removed by the hemofilter, HFR is hemofiltration rate, and %EL is the percentage of drug dosage removed by the hemofilter.

Statistical analysis was done using Wilcoxon rank sum test. Moderate significance was defined as $P < .1$, significance was defined as $P < .05$, and high significance was defined as $P < .01$.

## Results

Three patients were entered into the study: one male and two female, with heights of 75, 83, and 85 cm, and weights of 8, 16.4, and 13 kg respectively. All the patients had MODS and acute renal failure. Serum electrolytes, blood urea nitrogen, serum creatinine, liver function enzymes, albumin, and total protein were recorded daily during the study period. Multiple samples were obtained from each patient resulting in a total sample size of 16. Pharmacokinetic results are shown in Table 1.

The sieving coefficient for DOP was 0.92 ± 0.06; total plasma clearance was 25.3 ± 11.0 mL/kg/min. Clearance by hemofilter was 0.078 ± 0.011 mL/kg/min. Amount of drug removed by the hemofilter was 1363 ± 445 ng/min; and on average 0.56% of the DOP dose was removed by the hemofilter.

For DOB the sieving coefficient was 0.59 ± 0.09; total plasma clearance was 48.2 ± 9.4 mL/kg/min. Hemofilter clearance was 0.036 ± 0.008 mL/kg/min. Amount of drug removed by the hemofilter was 285 ± 99 ng/min; and on the average 0.13% of the DOB dose was removed by the hemofilter.

These results indicate that the amount of DOP and DOB removed by the hemofilter is negligible,

**Table 1. Pharmacokinetics of Dopamine and Dobutamine During Continuous Venovenous Hemofiltration**

| | SC | $CL_{HF}$ | $CL_{WB}$ | $EL_{HF}$ | %EL |
|---|---|---|---|---|---|
| Dobutamine, n = 10 | 0.590 | 0.036 | 48.20 | 285.0 | 0.130 |
| SE | ±0.090 | ±0.008 | ±9.400 | ±99.0 | ±0.400 |
| Dopamine, n = 6 | 0.920 | 0.078 | 25.30 | 1363.0 | 0.560 |
| SE | ±0.060 | ±0.011 | ±11.000 | ±445.0 | ±0.150 |
| P | <.05 | <.01 | NS | <.01 | <.01 |

SC, sieving coefficient; $CL_{HF}$, clearance by the hemofilter in mL/kg/min; $CL_{WB}$, total plasma clearance in mL/kg/min; $EL_{HF}$, amount of drug removed by the hemofilter in ng/min.

although in terms of clearance and percentage of dose removed DOB was filtered from the blood in greater amounts than DOB. Overall, the dosage of these drugs does not need to be altered during CVVH.

## Discussion

Since its introduction in 1977, continuous hemofiltration has gained wide popularity in the treatment of acute renal failure in critically ill pediatric patients, including neonates. The original technique was CAVH, but over the years new modalities have been developed, such as CVVH, continuous arteriovenous hemodiafiltration, and continuous venovenous hemodiafiltration (1,5).

Many of these patients also suffer from MODS and hemodynamic instability, requiring aggressive cardiovascular support with intravenous catecholamines. Because these patents are clinically unstable and require skillful and methodical medical management, it is imperative for physicians to know how hemofiltration affects the pharmacokinetics and pharmacodynamics of catecholamines in these patients.

To our knowledge, this is the first report studying the pharmacokinetics of DOP and DOB on pediatric patients with acute renal failure treated with CVVH. Plasma clearance for DOP and DOB in our study was similar to previous reports in the literature (6–7), validating our methodology and indicating that the pharmacokinetics of these catecholamines is not altered by CVVH. Of clinical significance was the very low clearance of DOP and DOB by the hemofilter and the small percentage of the drug dosage that is removed by the filter (%EL of 0.56 for DOP, and 0.13 for DOB). These findings suggest that both DOP and DOB are strongly bound to plasma proteins with a molecular weight > 10,000 d, which was the pore size of the filter. The protein binding of DOB was greater than for DOP, as evidenced by the greater clearance of DOP by the hemofilter. These findings might help explain previous reports in the literature showing that hemofiltration had little or no effect on cardiovascular hemodynamics in critically ill patients (2–3).

In conclusion, based on our results, we suggest that the dosage of DOP and DOB need not be altered on critically ill pediatric patients undergoing CVVH. However, additional studies are warranted to further characterize the pharmacokinetics of catecholamines during continuous hemofiltration.

## References

1. Smoyer WE, McAdams C, Kaplan BS, Sherbotie JR. Determinants of survival in pediatric continuous hemofiltration. J Am Soc Nephrol 6:1401, 1995
2. Bergstrom J. Catecholamines and control of blood pressure in hemodialysis and hemofiltration. Kidney Int 34:S110, 1988
3. Henderson LW. Heterogeneity of the cardiovascular response to hemofiltration. Kidney Int 29:901, 1986
4. Bickley SK. Drug dosing during continuous arteriovenous hemofiltration. Clin Pharm 7:198, 1988
5. Zobel G, Ekkehard R, Muller W. Continuous arteriovenous hemofiltration in premature infants. Crit Care Med 17:534, 1989
6. Zaritsky A, Lotze A, Stull R, Goldstein DS. Steady-state dopamine clearance in critically ill infants and children. Crit Care Med 16:217, 1988
7. Habib DM, Padbury JF, Anas NG, Perkin RM, Minegar C. Dobutamine pharmacokinetics and pharmacodynamics in pediatric intensive care patients. Crit Care Med 20:601, 1992