In Vitro Clearance of Antiepileptic Medications via Continuous Venovenous Hemofiltration

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Background

Neuroscience Intensive Care Units are increasing in number and are caring for a wider array of neurologically related critical illnesses with multi-organ dysfunction. Continuous renal replacement therapies (CRRT) are also more desirable than intermittent therapies in patients with acute neurology injury. As a result the need for CRRT is increasing in this setting. Since many of these patients require antiepileptic medications, an understanding of how CRRT may affect these medications is important.

Objectives

We tested three common antiepileptic medications in an in vitro continuous venovenous hemofiltration (CVVH) model to examine how the therapy affects medication levels. The sieving coefficients, filter absorption, and clearance of these medications were determined in this experiment.

Methods

We used the NxStage machine configured in CVVH with the NxStage System One CAR 500 polyethersulfone membrane. Samples were obtained from two machine runs. For each run the blood flow was 200 mL/min and replacement was 0.9% normal saline given pre-filter. The ultrafiltration rate was run at 1L/hr.

500 mg of valproic acid and levetiracetam and 250 mg of phenytoin were mixed in two liters of bovine blood bath containing 3.8% citrate and maintained at thirty seven degrees Celsius. The bath was connected to the patient access line and the patient return line connected to the bath. The effluent line went to a separate collection container.

Drug Sampling and Drug Concentration

Samples were collected pre-filter, post-filter and from the ultrafiltrate from both runs. The samples were then sent to an outside laboratory for measurement of drug concentration. The average of the runs was used in calculations. The sieving coefficient (SC), filter absorption (FA), and clearance (CL) for each drug were calculated from the following equations:

SC = (2 x concentration ultrafiltrate)/(concentration pre-filter + concentration post-filter)

FA = (concentration pre-filter – concentration post-filter)/concentration ultrafiltrate

CL = (ultrafiltrate rate) x SC x (blood flow rate/blood flow rate + replacement rate)

Results

Valproic Acid

- The sieving coefficient was 0.17
- Filter absorption was 14 percent
- Clearance was 2.43 ml/min

Phenytoin

- The sieving coefficient was 0.27
- Filter absorption was 4 percent
- Clearance was 3.86 ml/min

Levetiracetam

- The sieving coefficient was 0.14
- Filter absorption was 4 percent
- The clearance was 2.00 ml/min

Conclusion

In this model all three antiepileptic medications had sieving coefficients of less than 0.3, which is in range of reports using other filters. In this model phenytoin had the highest sieving coefficient and valproic acid had the most filter adsorption. Valproic acid, phenytoin and levetiracetam are antiepileptic medications often used in patients in neurocritical care units. All three medications have relatively low molecular weights. Valproic acid and phenytoin are highly protein bound and levetiracetam is not.

Valproic acid and phenytoin were cleared more than levetiracetam most likely due to saturation of protein binding sites and competition for protein binding sites.

This in vitro study suggests that antiepileptic medications are cleared by CVVH and in clinical practice following drug levels is reasonable.

Future Studies

- Future studies are warranted as an increasing variety of antiepileptic medications are being used in clinical practice.
- In patients receiving antiepileptic medications and on CRRT, we plan to follow drug levels closely and incorporate in vivo studies.

References

1. Davernport A. Seminars in Dialysis. 2009