Hemodiafiltration and High-Flux Hemodialysis Significantly Reduce Serum Valproate Levels Inducing Epileptic Seizures: Case Report

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Sir,

Valproate is used in the treatment of some forms of epilepsy. A recent review of antiepileptic drugs in patients with kidney disease [1] reports that dose supplementation after hemodialysis (HD) is not routinely recommended. It refers to some rather old literature, reporting that (low-efficiency) dialysis removes only 20% of administered valproate dose [2] and that (low-efficiency) HD (combined with hemoperfusion) produces only a transient drop in valproate concentration [3]. A significant removal of valproate with (high-efficiency) HD has been reported in recent years, but only in cases of valproate intoxication at serum concentrations up to 10 times therapeutic levels [4, 5]. The previously mentioned review therefore remarks that the effect of high-efficiency HD on clearance and seizure activity in patients on chronic HD is not known.

We report a case of a 23-year-old female HD patient (dry weight 57 kg, primary renal disease focal segmental glomerulosclerosis) who has been on HD for 3 years. She has had epilepsy since the age of 5 years and was treated with enteric-coated valproic acid (Apilepsin®) 1,500–1,800 mg on the non-dialysis day, with an additional 150–300 mg on the dialysis day – taken before or during HD. As hemodiafiltration (HDF) was introduced in our center in 2006, she began to experience short partial complex seizures typi-

cally appearing after her HD sessions. At that time she was treated with postdilutional HDF, with 20 l infusate per 4.5-hour session, FX80 dialyzer (helixone, 1.8 m², Fresenius Medical Care, Bad Homburg, Germany), blood flow 300 ml/min, AVF as vascular access. Valproate concentrations were measured before and after HDF approximately every 2 weeks and were 666 ± 53 (range 567–750, therapeutic levels 345–690) $\mu\text{mol/l}$ before and 341 ± 63 (range 261–462) $\mu\text{mol/l}$ after HDF, which represents a $49 \pm 9\%$ (range 38–59%) decrease

($n = 9$). To reduce dialysis efficiency, she was then switched to high-flux HD with a shorter duration of 4 h and a smaller FX60 dialyzer (helixone, 1.4 m², Fresenius), blood flow 300 ml/min. Valproate concentrations were measured again, together with ammonia levels, and were 631 ± 80 (range 574–773) $\mu\text{mol/l}$ before and 362 ± 53 (range 295–440) $\mu\text{mol/l}$ after HD, which represents a $42 \pm 6\%$ (range 36–52%) decrease ($n = 5$) (fig. 1). Predialysis ammonia was 66 ± 18 (range 49–92, normal levels 9–33) $\mu\text{mol/l}$ ($n = 5$). Since val-

Fig. 1. Serum valproate levels before and after dialysis in our patient in the HDF and HD period.

proate levels before dialysis were already around the upper therapeutic limit or slightly above in spite of a reduced dialysis dose and ammonia levels were also increased, her antiepileptic therapy was gradually changed to levetiracetam (Keppra®) 2,000 mg/day, after which her condition has improved.

Valproic acid is a small molecule (MW 144.2) which it is highly bound to plasma proteins (80–95%) at therapeutic concentrations, which decreases at toxic levels [6], and reduced binding is described in patients with renal impairment [7]. It has a half-life of 10–20 h, its quite complex metabolism takes place in the liver, and some of the metabolites contribute to the clinical effect and toxicity [1, 6]. Although the correlation between serum concentrations, efficacy and toxicity is not precise [1, 6], serum levels are nevertheless used to avoid toxicity.

Although low molecular weight would make valproate dialyzable, high protein binding has the opposite effect. Clinically important removal of valproate with HD has until now only been described in sev-

eral cases of valproate intoxication [4, 5], while with low-efficiency dialysis no significant removal has been reported [2, 3]. This difference was partially attributed to reduced protein binding at toxic levels [5]. On the contrary, we have found an average 42% drop in valproate concentration with high-efficiency HD and 49% with HDF. This caused valproate levels to drop from an upper to a lower therapeutic range limit and also caused (or at least contributed to) the partial complex seizures. A rebound increase in serum concentration after discontinuation of dialysis is known from intoxication reports [5] and seizures could also be the result of a fast change in serum concentration.

To conclude, contrary to current knowledge, we found that both HDF and high-flux HD significantly reduce serum valproate levels not only at toxic but also at therapeutic levels. However, we have not done a formal pharmacokinetic study and no firm conclusions about dosing of valproate can be made, so further study is necessary.

References

- 1 Israni RK, Kasbekar N, Haynes K, Berns JS: Use of antiepileptic drugs in patients with kidney disease. *Semin Dial* 2006;19:408–416.
- 2 Marbury TC, Lee CS, Bruni J, Wilder BJ: Hemodialysis of valproic acid in uremic patients. *Dial Transplant* 1980;9:961–964.
- 3 Kandrotas RJ, Love JM, Gal P, Oles KS: The effect of hemodialysis and hemoperfusion on serum valproic acid concentration. *Neurology* 1990;40:1456–1458.
- 4 Kane SL, Constantiner M, Staubus AE, Meinelcke CD, Sedor JR: High-flux hemodialysis without hemoperfusion is effective in acute valproic acid overdose. *Ann Pharmacother* 2000;34:1146–1151.
- 5 Hicks LK, McFarlane PA: Valproic acid overdose and haemodialysis. *Nephrol Dial Transplant* 2001;16:1483–1486.
- 6 Zaccara G, Messori A, Moroni F: Clinical pharmacokinetics of valproic acid – 1988. *Clin Pharmacokinet* 1988;15:367–389.
- 7 Bruni J, Wang LH, Marbury TC, Lee CS, Wilder BJ: Protein binding of valproic acid in uremic patients. *Neurology* 1980;30:557–559.