THE DIURNAL FLUCTUATIONS IN FREE AND TOTAL SERUM VALPROIC ACID CONCENTRATION AT STEADY STATE IN EPILEPTIC CHILDREN

R. Robinson[1],S. Dhillon[2],A.Jones[3],H.B. Valman[3], J.A. Cromarty[2,4];Pharmacy Department, Whittington Hospital[1], London; Clinical Pharmacy Unit[2] and Paediatric Department[3], Northwick Park Hospital, Harrow and The School of Pharmacy, University of London[4].

Valproic acid (VA) a broad spectrum anticonvulsant is widely used in paediatrics. The clinical value of monitoring total serum VA levels is controversial. A proposed therapeutic range of total serum VA concentrations is 50-100 µg/ml (Schobben et al 1980). VA is 90% bound to albumin (total VA levels 80 µg/ml) and the binding is saturable at higher levels (Gugler and Mueller 1978). The clearance of VA is capacity limited and binding sensitive. The free fraction of the drug, which determines the free concentration may be the major determinant of the pharmacological effect. Recent binding studies in adults have demonstrated greater fluctuations in free VA concentrations when compared to total VA concentrations (Marty et al 1982, Riva et al 1983a) and similar fluctuations in free levels have been shown in children (Riva et al, 1983b).

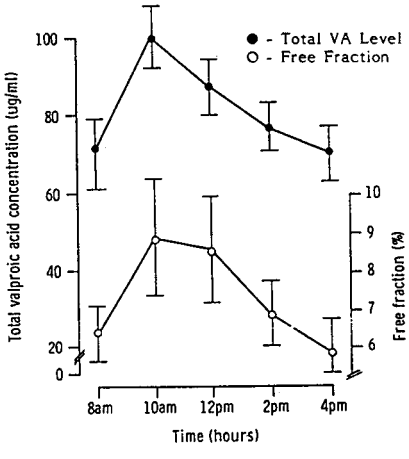
The present study investigated the fluctuations in free and total VA concentrations within a dosing interval in a group of epileptic children and assessed the influence of free fatty acids (FFA) on total and free VA concentrations.

Concentrations of free and total VA were measured in 9 children with epilepsy (3M, 6F mean age 9.8 ± 4.7 years). 6 patients were well controlled and 3 poorly controlled. All patients were receiving either a twice or three times daily regimen of sodium valproate, the duration of treatment being greater than 4 weeks. One patient also received carbamazepine.

Total and free VA concentrations at 0,2,4,6 and 8 hours post dose were measured using an enzyme immunoassay technique (EMIT and EMIT Freelevel System 1, Syva, U.K.) Fluctuations in free concentration throughout an 8 hour period 107 ± 31%, mean ± SD, n = 9) were almost double the fluctuations in total concentrations (55 ± 20%, n = 9) at the corresponding times. Fig. 1 illustrates the relationship between total VA level and free fraction. The free fraction is highest when the total concentration is the highest. Using analysis of covariance, a positive association was observed between free fraction and total concentration of VA in the combined data ($F = 49.5$ $p<0.001$). FFA concentration did not have a significant effect on the free fraction of VA ($F = 0.5$ NS).

There were no differences observed between the diurnal range of free VA concentration in patients who were well or poorly controlled. Alterations in the free fraction of VA with increasing total VA levels resulted in significant fluctuations in the free concentration. The larger than expected increase in free fraction of VA is probably due to a saturation in binding capacity. This study has shown that fluctuations in the FFA concentration do not significantly affect the free fraction of valproic acid and hence the total VA concentration is the major determinant of free fraction. Achievement of high "peak" total (and free) serum VA concentrations may be required for therapeutic efficacy. It remains to be assessed whether a free VA therapeutic concentration can be established.

Fig 1 Diurnal Fluctuations in Total VA Levels and Free Fraction [Mean ± SEM, n = 9]



Albani, F et al (1983) Epilepsea 24: 65-73
Gugler R. and Mueller G. (1978) Br. J. Clin. Pharmac. 5: 441-446
Marty J.J. et al (1982) Ibid 14: 339-404
Riva R. et al (1983a) Ther. Drug Monitor. 5: 191-196
Riva R. et al (1983b) Ibid 5: 197-200
Schobben F. et al (1980) Ibid 2: 61-71