AN IN-VITRO STUDY OF THE SERUM PROTEIN BINDING OF VALPROIC ACID IN PREGNANCY

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Valproic acid (VPA) is extensively bound (approx. 90%) to plasma proteins (Klotz and Antonin 1977; Gugler and Müller 1978; Patel and Levy 1979). The concentration dependence of this binding has been the subject of several studies (Gugler and Müller 1978; Patel and Levy 1979; Bowdle et al 1980), with marked reductions in protein binding occurring at high VPA concentrations, due to saturation of the drug binding sites on albumin.
Free fatty acids (FFA) are known to act as displacing agents of protein-bound VPA in-vitro (Monks and Richens 1979; Patel and Levy 1979; Riva et al 1982). Circulating levels of FFA are affected by pregnancy. Though the pattern of change is poorly documented, McDonald-Gibson et al (1975) reported that FFA levels are raised in late pregnancy. Riva et al (1984) recently suggested that the reduced VPA binding noted in pregnancy is mainly due to a reduction in albumin concentration, but may be influenced in the perinatal period by a marked elevation in maternal FFA.
This study therefore investigated in-vitro the effect of albumin, FFA and bilirubin on the serum protein binding of VPA, using samples from 15 pregnant women (38-40 weeks gestation); 15 age-matched women in established labour; and 15 age-matched non-pregnant controls. Protein binding was measured at 25°C (room temperature) using a rapid equilibrium dialysis/gas chromatographic technique.
Pregnancy was associated with a marked reduction in serum albumin (31.38 ± 1.60 g/l [mean ± SD] in labour; 31.25 ± 1.16 g/l in the third trimester), significantly lower than in non-pregnant controls (44.13± 1.96 g/l; $p<0.001$). FFA levels were significantly elevated in labour (0.94 ± 0.41 mmol/l) when compared to the third trimester (0.36± 0.23 mmol/l) and non-pregnant group (0.31 ± 0.21 mmol/l; $p<0.001$).
VPA serum protein binding exhibited concentration dependence from 20-100 mcg/ml in the labour serum pool; and at serum levels greater than 40 mcg/ml in the third trimester pool; but no concentration dependence was reported within the control serum. [The highest free VPA fractions at each total VPA level were consistently observed in the spiked labour pool].
Using individual serum samples, free VPA fraction was negatively related to the albumin level. For the labour serum samples, free VPA fraction correlated with FFA ($r = 0.756$; $p<0.05$; $n = 8$). No significant correlation was determined between free VPA fraction and bilirubin.
Free VPA fraction appears to be increased during pregnancy as a consequence of lowered albumin levels. An even greater increase in free fraction is seen in labour as a result of the influence of elevated free fatty acids. The clinical significance of these findings to both mother and foetus requires further investigation.

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