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Hyperammonaemia and hepatotoxicity during chronic valproate therapy: enhancement by combination with other antiepileptic drugs

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Erythrocyte (ENH_3) and plasma (PNH_3) ammonia levels, liver function tests and plasma valproate concentration were measured in 81 epileptic patients, comprising three therapeutic groups: Group 1 (23 patients) received sodium valproate (VPA) monotherapy, group 2 (33 patients) received sodium valproate combined with phenytoin, carbamazepine, phenobarbitone and/or primidone and group 3 (25 patients) received one or more of these anti-epileptic drugs without sodium valproate. The mean ENH_3 and PNH_3 of patients in group 1 (41.1 ± 30.7 μmol l^{-1} and 37.1 ± 31.8 μmol l^{-1}, respectively) and group 2 (44.5 ± 21.3 and 37.6 ± 21.4 μmol l^{-1}, respectively) were significantly ($P < 0.01$) higher than those in group 3 (28.7 ± 10.6 and 21.5 ± 7.8 μmol l^{-1}, respectively) and the reference range (30.1 ± 7.9 and 20.8 ± 5.7 μmol l^{-1}, respectively). Hyperammonaemia was more prevalent amongst patients in group 2, for both ENH_3 (45.5%) and PNH_3 (54.6%), than amongst patients in group 1 (30.4% and 52.2%, respectively) and group 3 (8% and 8%, respectively). There was a significant ($P \leq 0.05$) positive correlation between plasma VPA and total bilirubin concentrations. Chronic VPA therapy was also associated with an increase in bilirubin concentrations measured on average four months apart.

Keywords sodium valproate therapy plasma ammonia erythrocyte ammonia hepatic function

Introduction

Elevation of the plasma ammonia concentrations (PNH_3) have been documented during chronic sodium valproate (VPA) therapy in patients with and without encephalopathy, both when hepatic function was normal (Coulter & Allen, 1980; Murphy & Marquardt, 1982) and when it was abnormal (Willmore *et al.*, 1978; Young *et al.*, 1980; Marescaux *et al.*, 1982).

In a previous study of patients with liver disease, the erythrocyte ammonia level (ENH_3) was found to be a more accurate discriminator of portal-systemic encephalopathy (PSE) than the PNH_3 (Ratnaike *et al.*, 1983).

The aims of the present study were to determine the effects of chronic VPA and other anticonvulsant drug therapy on ENH_3 compared to PNH_3 concentrations and on hepatic function.

Methods

The study population consisted of 81 patients with epilepsy, attending the Neurology Outpatient Clinic at The Queen Elizabeth Hospital.

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Group 1

Twenty-three patients (10 males and 13 females, aged 8–30 years) received sodium valproate alone.

Group 2

Thirty-three patients (19 males and 14 females, aged 13–46 years) received sodium valproate and one or more other anticonvulsant drugs which included phenytoin, carbamazepine, phenobarbitone and/ or primidone.

Group 3

Twenty-five patients (13 males and 12 females, aged 14–77 years) received one or more other anticonvulsant drugs, which included phenytoin, carbamazepine, phenobarbitone and primidone but not VPA.

Blood samples were assayed for plasma concentrations of VPA, other anti-epileptic drugs (EMIT method, Syva, Palo Alto, California) and liver function tests (Technicon SMAC autoanalyser).

ENH_3 and PNH_3 were measured by a modification of the Hyland method (Buttery *et al.*, 1982), and patients were assessed clinically for PSE.

Results

The average duration of VPA therapy was 36 months and the average post-dose sampling interval was 4 h. The ENH_3 and PNH_3 concentrations are shown in Figure 1.

The mean erythrocyte and plasma ammonia concentrations for the three groups studied were as follows:

Group 1: ENH_3 was 41.1 ± 30.7 μmol and PNH_3 was 37.1 ± 31.8 μmol. Group 2: ENH_3 was 44.5 ± 21.3 μmol and PNH_3 was 37.6 ± 21.4 μmol; Group 3: ENH_3 was 28.7 ± 10.6 μmol and PNH_3 21.5 ± 7.8 μmol.

The mean ENH_3 and PNH_3 concentrations for groups 1 and 2 were significantly higher than the reference range and group 3 ($P < 0.001$, Mann-Whitney U test) but were not significantly different from each other. The results for group 3 were not significantly different from the reference range.

A greater number of group 1 and 2 patients had both ENH_3 and PNH_3 concentrations above the reference range than those in group 3 ($P < 0.01$, Fisher's Exact Test). Though no significant difference was observed there was a greater percentage of patients in group 2 above the reference range for both ENH_3 (15/33:45.5%) and PNH_3 (18/33:54.6%) compared to group 1

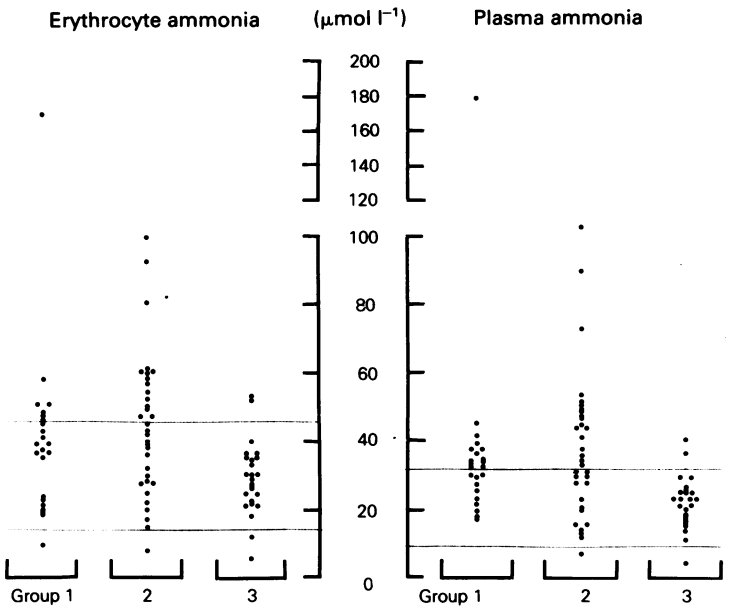

Figure 1 Erythrocyte and plasma ammonia concentrations in patients on anti-epileptic therapy. The horizontal lines indicate the reference range. The reference range for ENH_3 is 14.3–45.9 μmol l^{-1} (mean 30.1, s.d. + 7.9) and for PNH_3 9.4–32.2 μmol l^{-1} (mean 20.8, s.d. + 5.7).

(ENH_3 7/23:30.4%; PNH_3 12/23:52.2%) and group 3 (ENH_3 2/25:8%; PNH_3 2/25:8%).

Linear regression analysis was carried out between VPA, ammonia concentrations and liver function tests. There was only a significant positive correlation between the plasma VPA and the total bilirubin concentrations ($r = 0.256$, $P < 0.05$).

It is interesting to note that the patient in group 1, whose ENH_3 was 179 μmol l^{-1} and PNH_3 was 170 μmol l^{-1}, had no clinical evidence of PSE, nor were his liver function tests abnormal. Both his plasma creatinine and urea concentrations were normal.

Effect of duration of valproate therapy

Ten patients on VPA alone and 20 patients on VPA combination were investigated on two occasions, on average 4.3 months apart. There was no significant increase in either ENH_3 or PNH_3 (Wilcoxon's matched-paired signed-rank test). However, patients on VPA monotherapy showed a significant increase in the plasma concentrations of total bilirubin ($P < 0.001$, Wilcoxon's matched-paired signed-rank test), and conjugated bilirubin ($P < 0.001$). The alterations in biliburin concentrations were within the reference range except in one patient whose total bilirubin was elevated (24 μmol l^{-1}, reference range 1–20 μmol l^{-1}) and whose conjugated bilirubin rose to 10 μmol l^{-1} (reference range 0–5 μmoll^{-1}). In another patient albumin fell to 21 g l^{-1} (reference range 35–50 g l^{-1}).

Patients on VPA combination therapy ($n = 20$) also had significant increases in conjugated bilirubin ($P < 0.01$). An elevated conjugated bilirubin level (8 μmol l^{-1}) above the reference range occurred in one patient while elevations in lactate dehydrogenase (260 and 292 μ l^{-1}, reference range 120–250) were noted in two other patients and the albumin decreased (21 g l^{-1}) in a further patient.

Discussion

The high prevalence of hyperammonaemia in patients receiving VPA combination therapy in comparison to the other treatment groups may indicate a potentiating effect of VPA in elevating ammonia (Marescaux *et al.*, 1982; Warter *et al.*, 1983a). Anticonvulsants, such as phenytoin and phenobarbitone, may also contribute to VPA hepatic toxicity by causing enzyme induction (Jeavons, 1984).

In the present survey, the 53.4% PNH_3 elevation in patients on VPA is similar to that previously reported (Murphy & Marquardt, 1982). However, the clinical relevance of the elevated blood ammonia level remains obscure. Hyperammonaemia appears to enhance the depression of neurological, adrenal medullary and ileal function (Kuta *et al.*, 1984). The latter findings suggest that hyperammonaemia could be additive in the depression of hepatic and cerebral cell function due to VPA and its metabolites (Kesterton *et al.*, 1984). The measurement of ENH_3, was not superior to PNH_3 as a screening test for hyperammonaemia, as it was in a study of patients with PSE in liver disease (Ratnaike *et al.*, 1983).

Increased renal production of ammonia has been reported to be the cause of hyperammonaemia in VPA monotherapy (Warter *et al.*, 1983a), although an abnormality in hepatic urea formation has been postulated (Coude *et al.*, 1983). In this study, the presence of normal hepatic function tests in the patient with the highest blood ammonia levels, whilst taking VPA monotherapy, would be consistent with either a renal origin for the ammonia or subtle metabolic changes in the liver.

Coulter & Allen (1980) found that at a PNH_3 level of 60 μmol l^{-1}, patients exhibited signs of altered consciousness and therefore recommended a reduction in VPA dose at this PNH_3 concentration. In the present study there were four patients, all adults, whose PNH_3 concentration ranged from 73 μmol l^{-1} to 179 μmol l^{-1}. No reduction in VPA dose was considered necessary, as they exhibited no clinical evidence of PSE.

Effects of duration of therapy

Chronic VPA therapy, alone or in combination, was associated with a significant increase in plasma bilirubin. Indeed there was a positive correlation between the plasma valproate concentration and total bilirubin in all 56 patients treated with VPA. Elevation of the plasma bilirubin concentration has also been noted in acute hepatic dysfunction associated with chronic VPA therapy (Ware & Millward-Sadler, 1980). Isolated, dose-related elevation of serum levels of hepatic enzymes has previously been reported (Willmore *et al.*, 1978). However normal liver function has also been reported (Leary, 1982).

The present study has confirmed that chronic VPA therapy, alone or in combination, is associated with elevation of PNH_3 as well as ENH_3. The other significant findings include hyperbilirubinaemia during chronic VPA therapy and a positive correlation between plasma VPA and bilirubin concentrations. Our findings suggest a need for patients on chronic VPA therapy to have regular liver function tests performed.

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