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Decreased plasma protein binding of valproate in patients with acute head trauma

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1 One hundred and ten plasma samples were obtained from 50 patients treated with valproate for prophylaxis of post-traumatic head injuries. The samples were selected to include a wide range of albumin concentrations and were assayed for free and total valproate concentrations. Valproate binding parameters were determined from the Scatchard equation for one binding site using reweighted least squares analysis.

2 Plasma albumin concentrations were measured in 130 patients with head trauma. They started to decrease immediately after trauma, reaching a minimum at 5–7 days of approximately 24% of baseline value and did not return to normal until 1 month.

3 The free fraction of valproate varied six to seven-fold as albumin concentration ranged from 1.5 to 4.8 g 100 ml^{-1} (218–696 μmol l^{-1}). The mean association constant for binding (K_a) was 0.008 μmol l^{-1} and the mean number of binding sites (N) was 2.0. There values were similar to those reported for valproate in otherwise healthy patients with epilepsy.

4 Because of saturable protein binding of valproate, hypoalbuminaemia may necessitate the monitoring of free valproate concentrations to avoid toxicity when valproate is used in patients with acute head injury.

Keywords valproate protein binding hypoalbuminaemia head trauma

Introduction

There is a poor correlation between total plasma valproate concentrations and pharmacological effect [1]. Theoretically, valproate has pharmacokinetic properties consistent with a drug where monitoring of unbound plasma concentration is appropriate [2, 3]. Valproate is extensively bound to albumin (greater than 90%) within the range of concentrations found in patients and exhibits concentration-dependent protein binding when the total plasma concentrations exceed 555 μmol l^{-1} [4–7] . The degree of plasma binding of valproate is affected by conditions associated with altered albumin concentrations such as pregnancy [8], increasing age [9, 10], renal failure [11, 12] and hepatic disease [13]. Diurnal variation in plasma binding due to displacement of valproate by free fatty acids causes fluctuations in unbound plasma valproate concentrations that are twice those in total valproate concentrations [10, 14, 15]. In spite of suggested benefits of monitoring of free valproate concentrations, a relationship between free valproate concentrations and therapeutic effect has not been clearly demonstrated.

Two recent reports have indicated an association between valproate toxicity and increased unbound drug concentrations. In one study, replacement of carbamazepine with oxcarbazepine in patients on valproate resulted in valproate-related side effects. There was no change in the dose or total plasma concentration of valproate but the concentration of unbound valproate increased by 50% [16]. A case report described a patient with hypoalbuminaemia who developed significant neurotoxicity with a markedly elevated unbound valproate concentration (187 μmol l^{-1}), but a total valproate concentration

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only slightly above the recommended therapeutic range [17].

At least two physiological changes could occur after an acute traumatic head injury that could cause an increase in the free fraction of plasma valproate; namely increased plasma free fatty acids and decreased albumin concentrations. Griebel *et al.* [18] reported a lack of effect of trauma on free fatty acid concentrations in a group of paediatric patients. As part of the acute phase reaction following traumatic head injury, plasma albumin concentrations decrease over time [19, 20]. A two-fold increase in the free fraction of phenytoin following head injury has been reported in small numbers of adult [21, 22] and paediatric patients [18]. However, there are no data available on the effect of head injury on the plasma protein binding of valproate. Previous studies of the plasma binding of valproate in patients with hypoalbuminaemia, have included only two patients with albumin concentrations less than 435 μmol l^{-1}. Both of these cases had liver disease associated hypoalbuminaemia and their free drug fractions were 0.34 and 0.42 [13].

Because of the lack of valproate binding data in patients with severe hypoalbuminaemia, the aim of this study was to determine the effect of trauma-induced changes in albumin concentrations on the plasma binding of valproate.

Methods

Plasma albumin concentrations were measured in 130 patients with acute head trauma on the day of injury (baseline), on days 4, 14 and at 1 month after injury as part of the study design. Additional albumin concentrations were measured clinically for 100 of the 130 patients who remained in hospital due to their injuries. All patients (age > 18 years) who entered the emergency trauma centre at Harborview Medical Center with any of the following conditions were considered eligible: cortical confusion, depressed skull fracture, subdural haematoma, epidural haematoma, intracerebral haematoma, penetrating head wound, early seizures (within 24 h of injury). All patients had normal renal and hepatic function at time of sampling. Patients were not receiving any parenteral nutrition or other drugs known to alter the plasma binding of valproate (e.g. salicylic acid). The patients were 42 ± 23 (mean ± s.d.) years old and were predominately male (5:1, male:female ratio). The study was approved by the institutional review board of the University and written consent was obtained from the subjects or their legal guardians. In eight of the acutely ill patients, fasting plasma concentrations of free fatty acids were measured at twice weekly intervals up to 1 month after trauma. All samples were stored at −20° C until assayed. Statistical analysis was performed using one way analysis of variance and Dunnet's multiple comparison test. A $P \leq 0.05$ was considered to be significant.

One hundred and ten plasma samples were selected from 50 patients to include a wide range of albumin concentrations. Total plasma valproate concentrations were measured by a capillary gas chromatographic method [23]. Free plasma valproate concentrations were determined as above after ultrafiltration using the Centrifree Micropartition system-1 (Amicon, Danvers, MA). Free fatty acids (FFA) were determined using a commercially available kit (Wako Chem. Co, Dallas, TX). The lower limit of detection for both free and total valproate was 1 μg ml^{-1} with an interday and intraday coefficient of variation less than 5%.

Total valproate concentrations (C), unbound valproate concentration (Cu), and albumin concentrations (P) were fitted using iteratively reweighted least squares regression analysis by the Scatchard equation [24] for a one-site binding model (equation 1) using the SYSTAT statistical package [25] in order to evaluate the number of drug binding sites per albumin molecule (N) and the association constant (K_a).

$$Cu = \frac{1}{2}\left[C\text{–NP–}\frac{1}{K_a} + \sqrt{\left(C\text{–NP–}\frac{1}{K_a}\right)^2 + \frac{4C}{K_a}}\right] \quad (1)$$

Results

As part of the acute phase reaction that occurs after trauma, plasma albumin concentrations decreased with time, but had returned to normal levels at 1 month (Figure 1). Plasma free fatty acids (FFA) were elevated above the normal range in only one of the eight patients in which they were measured. Free fractions increased from 0.07 at albumin levels greater than 500 μmol l^{-1} to greater than 0.40 when albumin concentrations were less than 300 μmol l^{-1}. Using the one-site binding model, the K_a was 0.008 μmol l^{-1}, and the mean number of binding sites was 2.0. Parameters could not be well differentiated using a two-site binding model as previously reported by

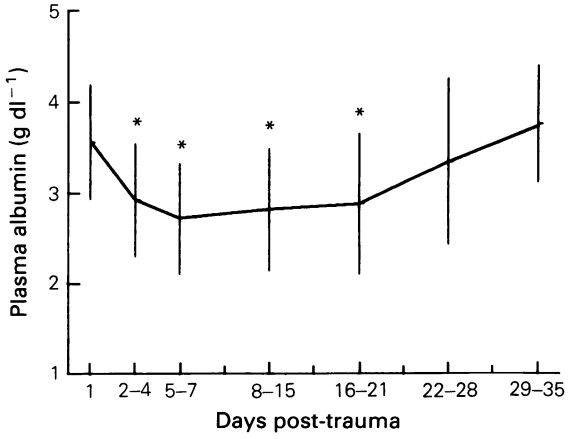

Figure 1 Change in mean (± s.d.) plasma albumin concentration after head injury (n = 130). *Statistically significant at the $P < 0.05$ level of significance using ANOVA and Dunnet's multiple comparison test.

Gugler & Mueller [12] using diluted plasma samples obtained from normal volunteers. Figure 2 shows the relationship between free valproate concentration and albumin concentration at a series of total valproate concentrations. Overall, the effect of increasing valproate concentration on free fraction was minimal when compared with the effect of decreasing albumin concentration.

Discussion

Hypoalbuminaemia induced by trauma was evident after 2–3 days and did not normalize until approximately 1 month in the critically ill patients. This is similar to the time course reported previously [20]. Our results confirm previous findings that the free fraction of valproate is inversely related to albumin concentration and suggest that the saturable protein binding of valproate results in a profound non-linear effect on valproate free fraction. The effect of hypoalbuminaemia on valproate binding was several fold greater than has been found for phenytoin in a similar population [18, 21, 22].

Valproate binding constants have been evaluated previously by Scatchard analysis in populations of otherwise healthy patients with epilepsy [7, 26–28].

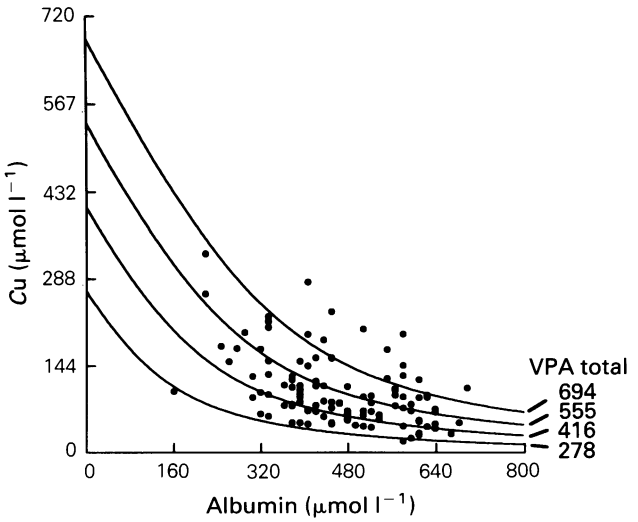

Figure 2 Relationship between plasma free concentration of valproate and albumin concentrations at various total plasma valproate concentrations.

In these studies, assessment of the relation between total and free concentrations of valproate was the primary objective and only a limited range of albumin concentrations was evaluated. Nevertheless, the association constant and number of binding sites reported were comparable with those found in our group of patients with head trauma. Thus, Yu [26] reported values of K_a = 0.005 μmol l^{-1} and N = 2.48 in 18 children with epilepsy. Scheyer *et al.* [7], found mean values of K_a = 0.013 μmol l^{-1} and N = 1.64 in 37 adults and showed that they were not influenced by concurrent therapy with carbamazepine or phenytoin. In addition, using population derived estimates obtained in seven adults (K_a = 0.0272 μmol l^{-1} and N = 3.2), Kodama *et al.* [27, 28] used the Scatchard binding equation to predict free valproate concentrations in 39 adults. As shown in Figure 2, the derived binding equation in this study appears consistently to underpredict the free valproate concentration at higher albumin concentrations, possibly due to a second binding site [7]. The use of the Scatchard binding equation to predict free valproate concentrations in acutely ill trauma patients with hypoalbuminaemia was not evaluated in this study.

Since valproate is an extensively metabolized low extraction drug, the increased free fraction in plasma observed after trauma should result in an increase in total drug clearance. However, the free drug clearance should remain constant. Therefore, since the effects of the drug may be related to drug concentration in plasma, adjustments of dosage based on the monitoring of total plasma drug concentration will be inappropriate. Two of our patients with plasma albumin concentrations less than 250 μmol l^{-1} had free plasma concentrations of valproate above 40 μg ml^{-1} but total concentrations within the target range. In both cases, the patients showed signs of valproate neurotoxicity (excess lethargy and tremor). Therefore, in patients who display toxic symptoms in spite of normal total valproate concentrations, it may be prudent to measure free valproate concentrations. As has been previously demonstrated for otherwise healthy patients with epilepsy, the Scatchard binding equation may be useful to predict free valproate concentrations in patients with hypoalbuminaemia induced by trauma.

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