

Valproate and protein binding – the importance of measuring free concentrations

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Background

Routine use of therapeutic drug monitoring (TDM) of antiepileptic drugs by measurement of total concentrations is well established in epilepsy. In cases where changes in protein binding affect highly bound drugs ($\approx 90\%$ for valproate), measurement of the unbound concentration will be more accurate for exposure of active drug in the body. The aim of this study was to describe current practice where unbound serum concentrations of valproate were measured and to discuss the clinical impact in patients with epilepsy.

Method

Retrospective, anonymous TDM-data from patients with measurements of unbound valproate concentrations were collected from the National Center for Epilepsy (2012-2017). The samples were taken drug-fasting in the morning at assumed steady-state. The study was approved by the Regional Ethics Committee.

Results

Data from 132 measurements in 81 patients using valproate were included, 40/60% women/men, average age was 39 (1-88) years.

Hypoalbuminemia, reduced renal function, intensive care monitoring, adverse effects, displacement interaction with stiripentol, young/old age and pregnancy (5 pregnancies in 3 women) were relevant reasons for the request.

The average dose of valproate was 1245 mg/day (72-3000) and total serum concentration of valproate was $82-908 \mu\text{mol/L}$ (reference range 300-700) (Figure 1a). Average unbound concentration was 20% (5-93, reference $\approx 10\%$) (Figure 1b).

Unbound concentrations of valproate increased up to 5-fold in two pregnancies from the first to the third trimester and decreased post-partum, reflecting an increased exposure where use of total concentrations would be misleading (Figure 2).

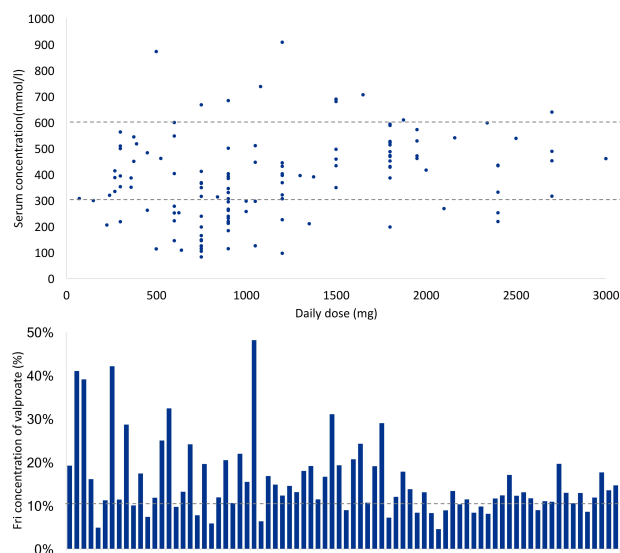


Figure 1a. Total serum concentration of valproate in relation to daily dose (n=132). 1b. Unbound concentration of valproate as percentage of total concentration in 78 patients.

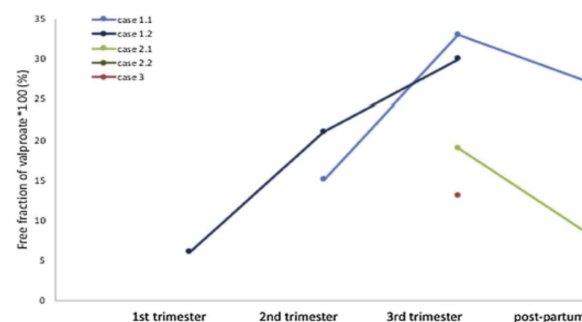


Figure 2. Changes in the percentage of unbound concentration of valproate in three women during five pregnancies, based on measurements of both total and unbound concentrations.

Conclusions

- ✓ Measurement of total and unbound concentrations of valproate showed increased free fraction in most of these vulnerable patients, and total concentrations may then underestimate drug exposure.
- ✓ Implementation of TDM with total and unbound concentrations may contribute to improved and tailored treatment for the individual patient.

