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Determinants of free serum valproate concentration: A prospective study in patients on divalproex sodium monotherapy

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ABSTRACT

Purpose: To evaluate variables affecting the valproate (VPA) free fraction and develop an equation for computing free VPA concentration from total VPA concentration.
Methods: Trough total and free VPA concentrations were collected from patients who participated in a prospective VPA monotherapy trial. All available paired data of trough total and free VPA concentrations were included. Significant variables from the univariate analysis were evaluated in a multivariate model.
Results: A total of 902 concomitant total and free VPA concentrations were available. Multivariate analysis showed that total VPA concentration, age and gender were significantly associated with VPA free fraction. However, the effect size of total VPA concentration was substantially higher than that of gender and age. VPA free fraction remained stable at around 10% for total VPA concentration between 20 and 60 μg/mL with subsequent linear increases for higher concentration. A scatter plot correlating total and free VPA concentrations showed that a quadratic equation best fitted the data, accounting for 88% of the free VPA concentration variance.
Conclusions: An increase in the total VPA concentration results in corresponding linear and non-linear rise in the VPA free fraction and free VPA concentration, respectively. The total daily dose of VPA should be increased in smaller increments whenever a total VPA concentration of 60 μg/mL is reached. When drug monitoring is needed, we recommend measuring the free VPA concentration. If this test is unavailable, and for patients with normal albumin levels, it can be predicted from the total VPA concentration using the generated equation.

1. Introduction

Therapeutic drug monitoring (TDM) for antiepileptic drugs (AEDs) is recommended in specific clinical situations to assess compliance, ensure therapeutic drug level, assist in the diagnosis of clinical toxicity, and guide dosage adjustment [1]. The reference range for trough total valproate serum concentration has traditionally been recognized to be between 50 μg/mL and 100 μg/mL (350 μmol/L to 700 μmol/L) based on the results of studies enrolling small number of patients maintained on VPA as part of a polytherapy regimen [2,3]. More recent data suggests that the total VPA concentration needs to be individualized with higher serum levels required to control focal onset seizures compared to primarily generalized tonic-clonic seizures [4]. On the other hand, higher total VPA concentration were found to be associated with more frequent and more severe adverse events [5] including a significant inverse linear correlation between total VPA concentration and platelet counts [6].

VPA has a complex pharmacokinetic profile. It is highly albumin bound [7,8] and the biologically active free VPA serum concentration varies non-linearly with increases in total VPA concentration [9–11]. It has therefore been suggested that measurement of the free VPA concentration is a better guide than total VPA concentration to reduce adverse events, improve seizure control, and avoid unwarranted dose adjustments [12,13].

The primary aim of this study was to evaluate the contribution and effect size of variables that could affect the VPA free fraction namely total VPA concentration, age and gender using data from a large cohort of patients who participated in a prospective randomized, double-blind, VPA monotherapy concentration-response design trial [5]. A secondary aim was to develop an equation that would allow computation of the free VPA concentration from the total VPA concentration.

2. Materials and methods

Patients 10 to 75 years of age, with a diagnosis of a localization related epilepsy and a documented history of at least two complex

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partial seizures per month while maintained on one AED (carbamazepine, phenytoin, primidone or phenobarbital) at therapeutic serum concentrations were eligible to participate in this study. Patients previously exposed to divalproex sodium (DVPX) and who failed to respond at serum VPA concentrations greater than 40 μg/mL (280 μmol/L) or with a history of intolerance to the drug were excluded. Also excluded were pregnant women, women of child bearing potential not practicing adequate birth control, patients with generalized seizures in the previous two years and those with major medical illnesses, psychiatric illnesses, or a history of pseudoseizures or non-compliance.

This was a randomized, double-blind, parallel group, multicenter, concentration-response design clinical trial that compared the safety and efficacy of two concentration ranges of DVPX [5]. All patients were administered Depakote^{R}, a delayed release formulation consisting of an oligomeric complex composed of sodium valproate and valproic acid in a 1:1 molar ratio twice daily. The Institutional Review Board at each center approved the study protocol, which was conducted in compliance with the US Food and Drug Administration regulations. More details about the trial design were previously published [5].

Patients were randomly assigned in a 1:1 ratio at each center into the high (80 to 150 μg/mL; 555 μmol/L to 1040 μmol/L) or low (25 to 50 μg/mL; 175 to 345 μmol/L) target trough serum VPA concentration groups. The study consisted of a baseline phase lasting eight to 12 weeks followed by a 24-week double-blind experimental phase. The experimental phase was divided into a dosage adjustment period (first eight weeks) followed by a 16-week dosage maintenance period. During the dosage adjustment period, the baseline AED was tapered and treatment with DVPX was initiated. DVPX dosage was gradually titrated upward to achieve the maximum tolerated serum concentration within the targeted range for each patient. To enter the 16-week maintenance period, patients had to be completely withdrawn from their baseline AED and be treated with DVPX as monotherapy. During this phase of the protocol, DVPX dosage was adjusted based on efficacy and tolerability, while maintaining trough serum VPA concentration within the targeted ranges.

Trough total and free VPA concentrations were determined from analysis of blood samples collected either eight to 15 h after the last DVPX dose, or less than one hour after the first dose of the day (taken before noon). All laboratory values were analyzed at a central laboratory, using a commercially available fluorescent polarized immunoassay. The minimum detectable assay limit of the apparatus was 13.0 μg/mL (90 μmol/L).

For each patient maintained on DVPX monotherapy we included all available paired data of trough total VPA concentration and free VPA concentration. The VPA free fraction was calculated as free VPA concentration divided by the corresponding total VPA concentration, and expressed as a percentage. Since many statistical models requires the assumption of linearity [14] and a non-linear association was previously reported between total VPA concentration and free VPA concentration [9,10], we initially performed the analysis using VPA free fraction as the dependent variable.

Descriptive statistics were reported as means with ranges for continuous variables and as frequencies for categorical variables.

Univariate linear regression analyses between age and total VPA concentration as the independent variables and VPA free fraction as the dependent variable were performed. A comparison between the means of VPA free fraction in men and women was performed using a two-sided *t*-test.

Significant variables from the univariate analysis ($p < 0.1$) were entered into a multiple regression analysis with VPA free fraction as the dependent variable. Values of significance were set at $P < 0.05$. The effect size (standardized coefficient) for the individual variables found to be significant in the multivariate model were calculated [15,16].

3. Results

During the 16-week dose maintenance phase (DVPX monotherapy phase), a total of 902 total VPA concentrations and concomitant free VPA concentrations were available for 228 (86%) out of the 265 patients enrolled in the double blind phase of the trial. There were 124 women and 104 men with a mean age of 35.1 years (range: 10–77 years). The mean values of total VPA concentration, free VPA concentration and VPA free fraction were 92.6 μg/mL (640 μmol/L), 18.3 μg/mL (130 μmol/L), and 17.0%, respectively.

Univariate linear regressions showed that both total VPA concentration (R = 0.764) and age (R = 0.094) were significantly associated with VPA free fraction. In addition, there was a gender difference with a significantly higher mean VPA free fraction in women (means = 17.6%) compared to that in men (16.2%; p = 0.004).

A multiple regression analysis showed that all three independent variables (total VPA concentration, age and gender) were significantly associated with the VPA free fraction (R = 0.782 and adjusted R-squared = 0.61). The effect size (standardized coefficient) for total VPA concentration, age, and gender were 0.771, 0.122, and 0.103, respectively. This implies that total VPA concentration was the most clinically relevant variable. Therefore, a plot of the mean VPA free fraction (with 95% confidence intervals) versus total VPA concentration at increments of 20 μg/mL (140 μmol/L) was performed (Fig. 1). As can be appreciated from this Figure, the mean VPA free fraction remains relatively constant at 10% for total VPA concentrations ranging between 20 and 60 μg/mL (140 μmol/L and 415 μmol/L), with a subsequent linear increase in the mean VPA free fraction for total VPA concentration above 60 μg/mL (415 μmol/L). For instance a rise in total VPA concentration from 70 μg/mL (485 μmol/L) to 110 μg/mL (765 μg/mL) (representing a 57.1% relative increase) was associated with an increase in the VPA free fraction from 12.5% to 18.9% (representing a 51.2% relative increase; Fig. 1).

Since the free VPA concentration equals the product of total VPA concentration and VPA free fraction, the increase in total VPA concentration is associated with a non-linear increase in the biologically active free VPA concentration. In the previous example

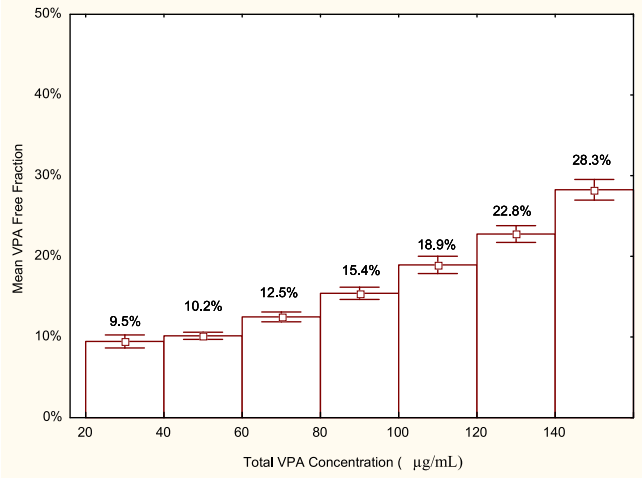

Fig. 1. Mean VPA free fraction (with 95% confidence intervals) within specific total VPA concentration ranges.