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Valproate Free Serum Concentrations: More Complex Than Simple Formulas

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Dear Editor

We read with interest the recent manuscript by Nasreddine et al [1] reporting total and free valproate concentrations from a randomized, double-blind, parallel group, multicenter, concentration-response design clinical trial that compared the safety and efficacy of two concentration ranges of divalproex. From the 265 adult and pediatric subjects enrolled in that trial, 902 synchronous values for total and free valproate concentration were obtained from 228 subjects. These data provided the basis for Nasreddine et al to perform multivariable analysis, which identified the significant impact that total valproate concentration had upon the free valproate concentration (standardized coefficient = 0.77) compared to the lesser effects from age (standardized coefficient = 0.12) or gender (0.10). A second degree polynomial equation was constructed [$y=(0.0016 * X^2) + (0.012 * X) + 0.4314$] where X equals the total valproate concentration in mg/L and Y equals the free valproate concentration in mg/L with excellent fit to the data (R-squared=0.878).

An accurate formula that predicts free valproate concentration is needed because only 2% of laboratories offer free valproate concentration assays and therapeutic drug