Therapeutic drug monitoring (TDM) is recommended during valproic acid (VPA) use, and total serum concentration has been widely adopted. However, the free form of VPA is responsible for its pharmacologic and toxic effects, and the total and free concentrations are highly discordant because of VPA's highly protein bound and saturable binding characteristics. Therefore, free VPA monitoring is increasingly advocated. Nevertheless, the correlation between free VPA concentration and associated adverse effects remains unknown.

A prospective cohort study enrolled adult patients undergoing VPA therapy with TDM. Patient characteristics, VPA use, and adverse effects (thrombocytopenia, hyperammonemia, and hepatotoxicity) were recorded. A multivariate logistic regression model was applied to identify the predictors of adverse effects, and the receiver operating characteristic curve was applied to locate the cutoff point of free VPA concentration.

A total of 98 free serum concentrations from 51 patients were included for final analysis. In total, 31 (31.6%), 27 (27.6%), and 4 (4.1%) episodes of hyperammonemia, thrombocytopenia, and hepatotoxicity were observed, respectively. Free VPA concentration was a predicting factor for thrombocytopenia but not for hyperammonemia. A free VPA concentration of >14.67 mcg/mL had the greatest discriminating power (area under the curve = 0.77) for the occurrence of thrombocytopenia.

A free VPA serum concentration of 14.67 mcg/mL had the optimal discriminating power for the occurrence of thrombocytopenia. Ammonemia should be monitored even if free VPA concentration is within the safety range [1].

1)
Tseng YJ, Huang SY, Kuo CH, Wang CY, Wang KC, Wu CC. Safety range of free valproic acid serum concentration in adult patients. PLoS One. 2020;15(9):e0238201. Published 2020 Sep 2. doi:10.1371/journal.pone.0238201