Is your patient's valproic acid dosage too low or high? Adjust it with this equation

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Valproic acid (VPA) often is used to treat mania in bipolar disorder, and it has a therapeutic range of 50 to 125 μg/mL of total serum concentration.[1] VPA binds highly to albumin, resulting in free drug concentrations (5 to 15 mg/L) that are responsible for its therapeutic effect.[2] Monitoring total VPA levels in patients with hypoalbuminemia could reveal seemingly subtherapeutic VPA levels, which could lead to unnecessary dosage adjustments or drug toxicity. Hermida et al[3] devised a correction equation to normalize total VPA serum concentrations <75 μg/mL in patients with hypoalbuminemia (*Table 1, Box*).

We present a case employing this equation in a patient with reported results and validation.

Case

Ms. T, age 75, is admitted to the hospital with delusional, paranoid, assaultive, and combative behavior. By applying Ms. T's baseline lab findings (*Table 2, page e2*) to the equation, a normalized total VPA level and estimated free VPA level of 70 μg/mL and 7 μg/mL, respectively, can be approximated. These estimates fall within the therapeutic range and are validated by the measured free VPA level of 9 μg/mL. Her VPA dosage is increased from

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Table 1

Relationship between free valproic acid fraction (α) and serum albumin concentration

Albumin (mg/L)	α (%)
4.2	6.5
4.1	6.8
4.0	7.3
3.9	7.9
3.8	8.5
3.7	9.1
3.6	9.8
3.5	10.5
3.4	11.3
3.3	12.1
3.2	13.0
3.1	14.0
3.0	15.0
2.9	16.2
2.8	17.4
2.7	18.7
2.6	20.1
2.5	21.6
2.4	23.2
2.3	24.9
2.2	26.8
2.1	28.9
2.0	31.0
1.9	33.3
1.8	35.8

Source: Adapted from reference 3

Box

VPA correction equations

Normalized total VPA concentration:
$$C_N = \alpha_H C_H / 6.5$$
VPA free fraction (%):
$$\alpha_H = C_F / C_N$$

Equation definitions:
C_N: normalized concentration of total VPA
α_H: VPA free fraction
C_H: measured total drug concentration of VPA
6.5: free fraction of VPA; albumin of 4.2 mg/L (normalized)
C_F: measured free drug concentration of VPA

VPA: valproic acid

Source: Adapted from reference 3

250 mg, 3 times a day, to 375 mg, twice a day, with an additional mid-day dose of 250 mg. Ms. T's behavioral symptoms improved 3 days following the increase to her VPA dosage, although she continued to show some confusion.

VPA serum levels should be assessed 2 to 4 days after initiation or dosage adjustments.[1] Also, consider patient-specific goals and intended clinical effect when adjusting VPA dosage. In practice settings, where free VPA levels are not routinely monitored or are cost prohibitive, this equation can guide clinical decision-making.[3]

When VPA levels are not routinely monitored or are cost prohibitive, this equation can guide clinical decision-making

Table 2

Ms. T's baseline lab findings

Laboratory test	Day 1	Day 2
Albumin (mg/L)	3.6	
VPA_F (μ/mL)		9
VPA_T (μ/mL)		46

VPA: valproic acid; VPA_F: free VPA concentration;
VPA_T: total VPA concentration;

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