Valproic acid

- Identification of Hub Genes and Prediction of Interacting Chemicals in Parkinson's Disease Using Bioinformatics
- Pharmacodynamic interactions between seletracetam and antiseizure comedications in the human photosensitivity model
- Risk factors for thrombocytopenia associated with intravenous valproic acid therapy in pediatric patients undergoing neurosurgical operations
- Valproic acid promotes transcriptional activation of Drd2 by mediating histone acetylation to inhibit the mTOR-Pttg1 signaling axis and exerts anti-PitNETs activity
- Nomogram for the prediction of valproic acid induced platelet decline: a nested case-control study
- Combined transcriptomic and proteomic analyses reveal relevant myelin features in mice with ischemic stroke
- SCN8A Epileptic Encephalopathy Mutation Displays a Loss-of-Function Phenotype and Distinct Insensitivity to Valproate
- Safety and Outcomes of Valproic Acid in Subarachnoid Hemorrhage Patients: A Retrospective Study

Valproic acid (VPA), is a histone deacetylase inhibitor.

Noninducer on liver cytochrome P450.

Recommended withdrawal period 2–4 weeks.

Levels of topiramate are reduced by other AEDs (phenytoin, carbamazepine, valproic acid and possibly others).

For patients on valproic acid (VA) alone, the maintenance dose of lamotrigine was 100–200mg/d (divided into 2 doses), and VA levels drop by ≈ 25% within a few weeks of starting lamotrigine. For patients on both enzyme-inducing AEDs and VA, the starting dose is 25mg PO qod × 2wks, then 25 mg q d× 2wks,then↑ by25–50 mg/d q 1–2 wks up to a maintenance of 100–150 mg/d (divided into 2 doses).

The number of female patients under 50 using valproate is decreasing over time. The 2018 European Medicines Agency referral procedure was followed by a notable reduction in female valproate users [1)].

Indications

Valproic acid indications

Dose

Adult range: 600–3000 mg/d. Peds range: 15–60 mg/kg/d. MDF= q d.

℞ Start at 15 mg/kg/d, increment at 1 wk intervals by 5–10 mg/kg/d. Max recommended adult dose: 60 mg/kg/d. If daily dose > 250mg is required, it should be divided. Supplied: Oral: capsules 250 mg.

Syrup 250 mg/5-ml. Depakote® (enteric coated) tabs: 125, 250, & 500mg; sprinkle capsules 125 mg. IV: Depacon® for IV injection 500 mg/5 ml vial.

Side effects

Serious side effects are rare. Pancreatitis has been reported, sometimes life-threatening. Fatal liver failure has occurred especially if age < 2 yrs and in combination with other AEDs. Teratogenic .

Drowsiness (temporary), minimal cognitive deficits, N/V (minimized with Depakote), liver dysfunction, hyperammonemia (even without liver dysfunction), weight gain, mild hair loss, tremor (dose related; similar to benign familial tremor; if severe and valproic acid is absolutely necessary, the tremor may be treated with beta blockers). May interfere with platelet function, caution with surgery on these patients.

Contraindications

✖ Pregnancy: causes neural tube defects (NTD) in ≈ 1–2% of patients. Since a correlation between peak VA levels and the risk of NTDs has been found, if VA must be used, some experts recommend changing from BID to TID dosing. ✖ Patients ≤ 2 yrs of age (risk of hepatotoxicity).

Complications

Valproic Acid Complications.

Safety range of free valproic acid serum concentration in adult patients

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 valproic acid (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 [2].

References

1)
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2)
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