

Valproate Induced Tremors

Tremors are a neurological condition characterized by rhythmic shaking movements in different parts of the body. Valproate induced tremors (VIT) affecting 6-64% of patients. They are the most common neurologic adverse events observed with valproate. They are most often observed with action or postural in nature, although a resting tremor may occur.

Clinical Presentation

- VIT is fine in nature. It can affect a patient's head, mouth, tongue, and limbs. It is most common in the upper limbs, yet can also involve the lower limbs.
- VIT shares clinical and electrophysiological features of an essential tremor and may exacerbate any underlying pathology.
 - Essential tremor: Common neurological condition that causes involuntary, rhythmic shaking primarily in the hands and arms during movement. It can also affect the head, voice, or legs.

Dosing and Formulation

- Differences between peak-trough levels in controlled-release valproate versus conventional formulations may attribute to the development of tremors in taking valproate.
- Valproate tremor is fully reversible with discontinuation of valproate treatment.

Assessment

Patient factors

- Personal or 1st degree family history of essential tremors, hyperthyroidism, alcohol or benzodiazepine withdrawal, excessive caffeine intake, and many types of anxiety. Elderly and people of male gender are at increased risk.

Medications

- Sympathomimetics, use of decongestants, inhaled B-2 agonists, psychostimulants, norepinephrine reuptake inhibitors and caffeine.
- Others include lithium, lamotrigine, D2 antagonist/partial agonists (i.e. haloperidol/aripiprazole).

Treatment Strategies

First-Line Adjustments

- Treat the patient, not the level.
 - Greater than 90% of the medication is bound to plasma proteins. Binding decreases with increasing valproate concentrations as well as the presence of other plasma protein bound medications.
 - Monitor for drug-drug interactions may reduce the presence of co-occurring tremors.

- Dose adjustments may be required when given with other CYP450 inhibitors.
- Implement gradual dose changes.
- Reduce serum level while maintaining therapeutic efficacy. Therapeutic range for total valproate in epilepsy is 50 to 100 mcg/mL and in mania can be higher up to 125 mcg/mL.

Pharmacological Intervention

- Beta-blockers are the first line medication treatment option.
 - Propranolol 20-100 mg divided doses.
- Alternative medication interventions:
 - Primidone 100-750 mg/day, most respond to doses \leq 250 mg/day. Approximately 15% of primidone is converted to phenobarbital, a potent hepatic inducer that can lower drug levels of concomitant medications.
 - Amantadine 100 mg twice daily. **Note: Evidence supporting use for tremor is mixed.*

References

Canning, J. E., Burton, S., & Hall, B. (2012). Lithium and valproate-induced tremors. *Mental Health Clinician*, 2(6), 174–176. <https://doi.org/10.9740/mhc.n117498>

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