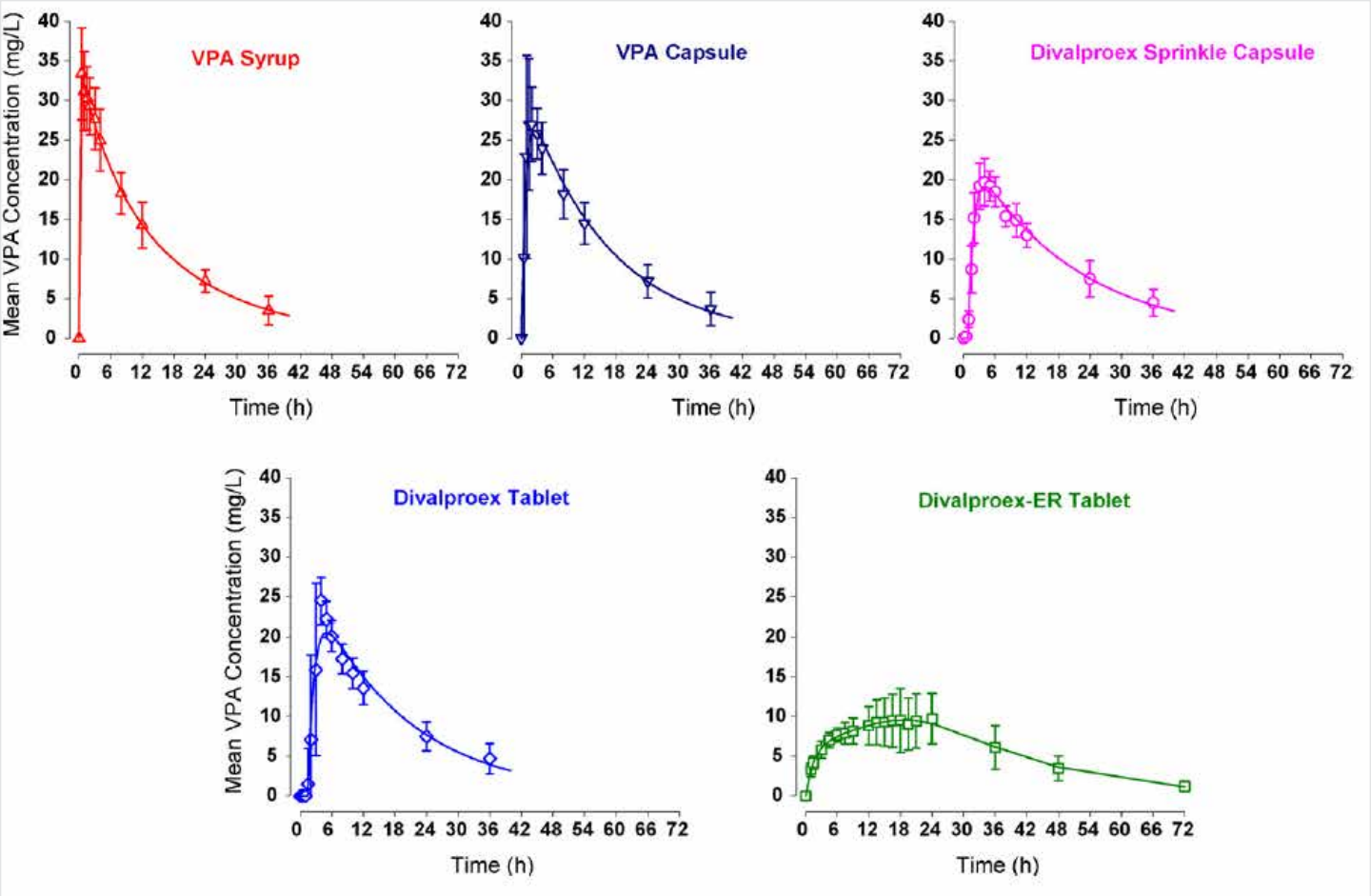
Valproic Acid/Divalproex

Mechanism of Action

Inhibition of voltage-gated sodium channels, increased GABAergic transmission, inhibition of histone deacetylase, and modulation of calcium channels involved in neuronal signaling

Pharmacokinetics

Pharmacokinetic model predictions and observed plasma VPA concentration-time profiles over 72h for five oral VPA/ divalproex formulations following a 250 mg single dose. Symbols and error bars represent mean ‡ standard deviation. Lines represent the model fit to the mean data.



Dutta S, Reed RC. Distinct absorption characteristics of oral formulations of valproic acid/divalproex available in the United States. Epilepsy Res. 2007 Mar;73(3):275-83. doi: 10.1016/j.eplepsyres.2006.11.005. Epub 2007 Jan 8. PMID: 17208410.

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Sublinear Pharmacokinetics

At lower concentrations, changes in the dose will not yield proportional increases in the total plasma level. Thus, doubling the dose will not double the blood level when the concentration is small. However, beyond 100 mcg/ml, free valproate levels will increase exponentially with small dose changes due to saturation of plasma proteins. At higher concentrations, dose changes need to be smaller to avoid toxicity.

Indications

Seizures, bipolar disorder, and migraines. Off label: status epilepticus, neuropathy, agitation/aggression, acute phases of schizoaffective disorder and schizophrenia, mixed episodes, severe self-injurious behaviors.

Absolute Contraindications

Pregnancy, hypersensitivity, unstable liver disease and Child-Pugh C, mitochondrial disorders, urea cycle disorders, pancreatitis, severe thrombocytopenia, and children < 2 years old.

Black Box Warnings

Teratogenicity, mitochondrial disease, pancreatitis, < 2 years old are at increased risk of fatal hepatotoxicity.

Precautions

Females of childbearing age not receiving reliable contraception, concomitant use of myelotoxic agents, myelosuppression, coagulation disorders, elderly, hypoalbuminemia, acute TBI, bariatric surgery, hypothermia, males planning to have children within 3 months of exposure.

Initial workup

CBC with diff, LFTs, B-HCG, EKG, weight/BMI, waist circumference, consent.

Initiation

Bipolar disorder and other psychiatric indications: For VPA syrup, VPA capsule, divalproex sprinkles, and divalproex DR: 750 mg in divided doses. For divalproex ER: 25 mg/kg/day once a day. The dose of Divalproex ER needs to be 8-20% higher due to lower bioavailability. There is no need for prolonged titrations. Target level: 80-120 mcg/ml. This is the range required for most psychiatric conditions.

Acute mania or mixed states: Valproic acid/divalproex can be loaded with 20 – 30 mg/Kg/day (divided doses for all formulations except ER), obtain level between 4-7 days, and target concentrations of 100-120 mcg/ml (acute mania).

Seizure disorders: initial dose 10 – 15 mg/kg/day, given in 2-3 divided doses (once a day for ER). Increase by 5-10 mg/kg/week. Max: 60 mg/kg/d. Target level: 50 – 100 mcg/mL (note: this range does not apply to psychiatric disorders).

Free valproate levels: if there are concerns of toxicity or poor benefit despite levels within range, measure free valproate levels. Range: 7-23 mcg/ml (see sublinear pharmacokinetics above).

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Different Formulations

Oral formulation	Potential Advantage	Clinical Considerations	Divided Doses	Dose Adjustment
VPA syrup	Poor adherence, feeding tubes, dysphagia, pediatric Fast absorption (useful when high concentrations need to be reached rapidly)	Taste Variable/poor absorption Dose adjustment needed Divided dosing GI side effects	Yes	Recent data indicates possible need to increase dose by 10-30% when switching from other formulations to solution
VPA capsule	Previously tolerated Patient preference	Divided dosing. GI side effects	Yes	When switching from ER
Divalproex sprinkles	Patients with poor adherence. Pediatric and geriatric More palatable than syrup	Divided dosing GI side effects	Yes	When switching from ER
Divalproex DR	Individuals prone to GI side effects	Divided dosing	Yes	When switching from ER
Divalproex ER	Only formulation that can be given once a day GI side effects are less likely Stable plasma concentrations	Large pills. Less suitable for patients with dysphagia Slightly lower bioavailability	No	Increase dose by 8-20% when switching from other formulations to ER

Monitoring Summary

Recommended times	Tests
Baseline	CBC with differential, LFTs, Pregnancy test, ECG (past year)
Monthly up to 6 months	CBC with differential, LFTs, amylase, lipase
From 6 months onward	CBC with differential, LFTs, amylase, lipase, VPA plasma concentration, ECG (Q6-12 months), annual physical exam (females)

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Adverse Effects

- GI symptoms. Delayed release and extended-release formulations carry less incidence of GI side effects.
- Neural tube defects, neurodevelopmental disorders, and decrease in IQ scores. Avoid in pregnant women and childbearing age without reliable contraception. This is mitigated but not eliminated by folic acid.
- Pancreatitis. This is not a dose related risk. Discontinue medication. Do not re-challenge.
- Thrombocytopenia. Dose-related risk. Risk increases >110 mcg/mL (females) and 135 mcg/mL (males). Risk of bleeding begins < 50,000/mm3. Lower dose, limit polypharmacy, increase monitoring. Discontinue if persistent decline.
- Risk of hepatotoxicity and acute liver failure, usually occurring within the first six months. Higher risk in patients with mitochondrial disease.
- Hyperammonemia and hyperammonemic encephalopathy.
- Weight gain (10% occurrence with average of 5.5 pounds).
- Sedation, tremor, vision changes, ataxia, nystagmus, irritability, and suicidal ideation
- Flu like symptoms and rhinitis.
- Alopecia, nail pigmentation, edema, and weight loss.
- Probable association with polycystic ovary disease.

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