VALPROATES
divalproex sodium
div-ah-val-proe-es ek-soe-id-um)
Depakote, Depakote ER, Depakote Sprinkle, Epival
valproate sodium
(val-proe-at-soe-id)
Depacon
valproic acid
(val-proe-ik-as)
Depakene
Classification
Therapeutic: anticonvulsants, vascular headache suppressants
Pregnancy Category D, X (migraines)

Indications

Action
Increase levels of GABA, an inhibitory neurotransmitter in the CNS. Therapeutic Effects: Suppression of seizure activity. Decreased manic episodes. Decreased frequency of migraine headaches.

Pharmacokinetics
Absorption: Well absorbed following oral administration; divalproex is entericoated, and absorption is delayed. ER form produces lower blood levels. IV administration results in complete bioavailability.

Distribution: Rapidly distributed into plasma and extracellular water. Cross blood-brain barrier and placenta; enters breast milk.

Protein Binding: 80–90%, decreased in neonates, elderly, renal impairment, or chronic hepatic disease.

Metabolism and Excretion: Mostly metabolized by the liver; minimal amounts excreted unchanged in urine.

Half-life: Adults: 9–16 hr.

TIME/ACTION PROFILE (onset = anticonvulsant effect; peak = blood levels)
ROUTE ONSET PEAK DURATION
PO—liquid 2–4 days 15–120 min 6–24 hr
PO—capsules 2–4 days 1–4 hr 6–24 hr
PO—delayed-release products 2–4 days 3–5 hr 12–24 hr
PO—extended-release products 2–4 days 7–14 hr 24 hr
IV 2–4 days end of infusion 6–24 hr

Contraindications/Precautions
Contraindicated in: Hypersensitivity; Hepatic impairment; Known/suspected urea cycle disorders (may result in fatal hyperammonemic encephalopathy); Mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma (risk for potentially fatal hepatotoxicity); Pedi: Children ≤ 2 yr with suspected mitochondrial disorder caused by mutations in mitochondrial DNA polymerase gamma (risk for potentially fatal hepatotoxicity); OB: Pregnancy (for migraines only).

Use Cautiously in: All patients (may risk of suicidal thoughts/behaviors); Bleeding disorders; History of liver disease; Organic brain disease; Bone marrow depression; Renal impairment; Women of childbearing potential; Geri: Risk of adverse effects; OB: Use during pregnancy is linked to congenital anomalies, neural tube defects, abortion, and spontaneous abortions in the mouse as well as impaired cognitive development in the child matures. Women with extreme caution.

Adverse Reactions/Side Effects
CNS: suicidal ideation and attempts, aggression, disinhibition, headache, insomnia, sedation, confusion, depression, CV: peripheral edema, EENT: visual disturbances, GI: hepatotoxicity, pancreatitis, abdominal pain, anorexia, constipation, nausea, vomiting, constipation, cutaneous congestive urticaria, derm: alopecia, rashes, endo: weight gain.

Overdosage:
CNS: sedation, respiratory depression, coma, extrapyramidal symptoms, convulsions, respiratory depression, vomiting, urticaria, dermatologic reactions. Treatment: Supportive. Seizures: Management of status epilepticus: General supportive measures. Treatment with diazepam or midazolam may be considered until convulsions can be controlled.

Protein Binding: 80–90%, decreased in neonates, elderly, renal impairment, or chronic hepatic disease.
**Drug-Drug:** Risk of bleeding with warfarin. Blood levels and toxicity may be ↑ by aspirin, carbamazepine, chlorpromazine, cimetidine, phenytoin, or rifampin. ↑ USP depression with other CNS depressants, including alcohol, an- thistamines, antihypertensives, opioid analgesics. MHD inhibitors and other antiprostaglandin inhibitors, including cyclo-oxygenase inhibitors, may ↓ acute thrombocytopenia; ↓ threshold and effectiveness of aspirin. Carbamazepine, meclofenamate, phenytoin, and rifampin may ↓ valproate blood levels. Valproate may ↑ toxicity of barbital, ethosuximide, lamotrigine, phenobarbital, phenytoin, topiramate, or zolpidem. Concurrent use with thiopental may ↑ risk of hypoglycemia and hyperammonemia; use with or without excretion inhibitor. Ertapenem, imipenem, or meropenem may ↓ valproate blood levels.

**Route/Dosage:**

**PO (Adults and Children):** Initial dose of 10–15 mg/kg/day in 1–4 divided doses; ↑ by 5–10 mg/kg/daily weekly until therapeutic response achieved (not to exceed 60 mg/kg/day). When daily dose exceeds 250 mg, given in divided doses.

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**PO (Adults and Children):** Give same daily dose and at same frequency as was given prior to and periodically during therapy. May cause leukopenia and thrombocytopenia. Blood levels and toxicity may be ↑ by 5–10 mg/kg/day weekly until therapeutic response achieved (not to exceed 60 mg/kg/day); when daily dosage exceeds 60 mg/kg/day, give in divided doses.

**Mood Stabilizer**

**PO (Adults):** Depakote—Initial dose of 750 mg/day in divided doses initially, titrated rapidly to desired clinical effect or trough plasma levels of 50–125 mcg/mL (not to exceed 60 mg/kg/day). Depakote ER—Initial dose of 25 mg/kg once daily, titrated rapidly to desired clinical effect of trough plasma levels of 90–125 mcg/mL (not to exceed 60 mg/kg/day).

**Migraine Prevention**

**PO (Adults and Children ≥6 yr):** Depakote—250 mg once daily (up to 1000 mg/day). Depakote ER—500 mg once daily for 1 wk, then ↑ to 1000 mg once daily.

**NURSING IMPLICATIONS**

**Assessment**

- **Neuro:** Monitor frequency and intensity of migraine headaches.
- **Geri:** Assess patients for excessive somnolence.
- **Mood Stabilizer:** Assess location, duration, and characteristics of serum activity. Initiate seizure precautions.
- **Migraine Prevention:** Assess mood, ideation, and behavior frequently.
- **Migraine Prophylaxis:** Assess frequency and intensity of migraine headaches.
- **Seizures:** Assess for suicidal tendencies, especially during early therapy. Restrict amount of drug available to patient. Risk may be increased in children, adolescents, and adults ≥6 yr.
- **Lab Test Considerations:** Monitor CBC, platelet count, and bleeding time prior to and periodically during therapy. May cause leukopenia and thrombocytopenia. May cause hepatic dysfunction. Monitor liver function tests.
- **Monitor hepatic function (LDH, AST, ALT, and bilirubin) and serum am- monium concentrations prior to and periodically during therapy. May cause hepatic/toxicity. Monitor closely, especially during initial 5–6 mos of therapy; fatalities have occurred. Therapy should be discontinued if hy- perammonemia occurs.
- **Geri:** Assess tolerance with caution of elderly patients.
- **Laboratory:** Monitor liver function tests.
- **Pharmacokinetics:** Therapeutic serum levels range from 50–100 mcg/ mL (50–125 mcg/mL for mania). Doses are gradually ↑ until a pre-dose serum concentration of at least 50 mcg/mL is reached. However, a good correlation among daily dose, serum level, and therapeutic effect has not been established. Monitor patients receiving near the maximum recommended 60 mg/kg/day for toxicity.

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Potential Nursing Diagnoses

Risk for injury (Indications)

Implementation

- Do not confuse Depakote ER and regular dose forms. Depakote ER produces lower blood levels than Depakote dosing forms. If switching from Depakote to Depakote ER, increase dose by 50%.

- Single daily doses are usually administered at bedtime because of sedation.

- PO: Administration with or immediately after meals to minimize GI irritation. Extended-release and delayed-release tablets and capsules should be swallowed whole, do not open, break, or chew, will cause mouth or throat irritation and destroy extended release mechanism. Do not administer tablets with milk or carbonated beverages (may cause premature dissolution). Delayed-release divalproex sodium may cause less GI irritation than valproic acid capsules.

- Shake liquid preparations well before pouring. Use calibrated measuring device to ensure accurate dose. Syrup may be mixed with food or other liquids to improve taste.

- Sprinkle capsules may be swallowed whole or opened and entire capsule contents sprinkled on a teaspoonful of soft, cool food (applesauce, pudding). Do not chew mixture. Administer immediately, do not store for future use.

- IV Administration

  - pH: 7.6

  - Intravenous Infusion: Diluent: May be diluted in at least 50 mL of D5W, 0.9% NaCl, or LR. Solution is stable for 24 hr at room temperature. Concentration: 2 mg/mL. Limit: Infuse over 60 min (20 mg/min). Rapid infusion may cause increased side effects. Has been given as a one-time infusion of 1000 mg over 5–10 min. 4–5 mg/kg/min up to 15 mg/kg in patients with uncontrolled seizures.

  - Y-Site Compatibility: cefepime, ceftazidime.

  - Y-Site Incompatibility: vancomycin.

Patient/Family Teaching

- Instruct patient to take medication as directed. If a dose is missed on a once-a-day schedule, take as soon as remembered. If on a multiple-dose schedule, take it within 6 hr of the scheduled time, then space remaining doses throughout the remainder of the day. Avoid withdrawal reactions in status epilepticus.

- May cause dizziness or drowsiness. Caution patient to avoid driving or other activities requiring alertness until effects of medication are known. Tell patient not to engage in driving or operating machinery or engaging in hazardous activities unless he or she determines that the patient can perform such tasks safely.

- Instruct patient to notify health care professional of all Rx or OTC medications, vitamins, or herbal products being taken and consult health care professional before taking any new medications, especially CNS depressants. Caution patient to avoid alcohol during therapy.

- Advise patient and family to notify health care professional if thoughts about suicide or dying, attempts to commit suicide; new or worse depression; new or worse anxiety; feeling very agitated or restless; panic attacks; trouble sleeping; new or worse irritability; acting aggressively; being angry or violent; acting on dangerous impulses; an extreme increase in activity and talking, either unusual changes in behavior or mood occur.

- Instruct patient to notify health care professional prior to treatment or surgery.

- Advise patient to notify health care professional if anorexia, abdominal pain, severe nausea and vomiting, yellow skin or eyes, fever, sore throat, malaise, weakness, facial edema, lethargy, unusual bleeding or bruising, pregnancy, or loss of seizure control occurs. Children 2 yr of age are especially at risk for fatal hepatotoxicity.

- May cause teratogenic effects. Instruct female patients to notify health care professional immediately if pregnancy is planned or suspected or if breast feeding. Advise pregnant patients taking valproates to enroll in the NAAED Pregnancy Registry by calling 1-888-233-2334; call must be made by patient or proxy. Registry Web site is www.aedpregnancyregistry.org.

- Advise patient to carry identification at all times describing medication regimen.

- Emphasize the importance of routine exams to monitor progress.
Evaluation/Desired Outcomes
● Decreased seizure activity.
● Decreased incidence of manic episodes in patients with bipolar disorders.
● Decreased frequency of migraine headaches.

Why was this drug prescribed for your patient?