

Background for Health Care Provider:

Valproic acid is almost completely absorbed from the small intestine and has 90% bioavailability in the divalproex sodium extended release form when given after a meal. Food may slow down absorption. For best therapeutic outcomes, patients should take the medication consistently with food. Once in the serum, valproic acid is approximately 90% protein bound. Since valproic acid is highly bound to plasma proteins, there may be some clinically significant binding interactions with other drugs. Additionally, elderly patients and those with hepatic impairment may also have higher unbound drug levels due to low albumin levels. Valproic acid is metabolized predominantly in the liver by glucuronic acid conjugation (40-50%), therefore apparent clearance of valproic acid is affected by the co-administration of drugs that induce or inhibit glucuronidation. Induction of glucuronidation will lead to decreased plasma valproic acid levels, whereas inhibition will lead to increased levels. Other metabolic pathways for elimination include: hepatic mitochondrial beta oxidation (40%), and microsomal oxidation to numerous metabolites (15% to 20%). Similarly, the apparent clearance of valproic acid can be affected by the co-administration of drugs that induce or inhibit either of the aforementioned pathways. Induction will lead to decreased plasma valproic acid levels, whereas inhibition will lead to increased levels.

Finally, valproic acid can inhibit some enzymes in the body. Specifically, cytochrome P4502C9, UDP-glucuronosyltransferase, and epoxide hydrolase can be inhibited. Inhibition can lead to increased levels of other drugs that are normally metabolized by these enzymes.

Effect of Other Drugs on Valproic Acid Serum Levels:

Decrease Valproic Acid Serum Levels

- Rifampin
- Combined Oral Contraceptives
- Carbamazepine
- Cholestyramine
- Macrolide Antibiotics
- Rifampin
- Ritonavir

Increase Valproic Acid Serum Levels

- Lamotrigine
- Felbamate
- Risperidone

Effect of Valproic Acid on Other Drugs' Serum Levels:

Increase Other Serum Drug Levels

- Amitriptyline
- Nortriptyline
- Carbamazepine
- Clomipramine
- Phenobarbital
- Primidone
- Phenytoin
- Lorazepam

Decrease Other Drug Levels

- No known clinically significant interactions

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