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Bipolar Disorders and Valproate: Pharmacokinetics,Pharmacodynamics, Therapeutic Effects and Indications of Valproate: Review of Articles

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Abstract

Valproate is a mood stabilizer which is approved for use in acute and maintenance mania. It is the first line drug for bipolar patients with presence rapid cycling, irritable mania, bipolar disorder with comorbid substance use disorders, severe mania with psychosis, mixed mania and secondary mania.

The specific mechanism of action of valproate in stabilizing mood is unknown. It exerts effects by enhancement of brain γ-aminobutyric acid (GABA) levels via multiple actions of synthesis and degradation, and modulation of other neurotransmitters, voltage sensitive Na+ channels, extra hypothalamic neuropeptides, secondary messenger systems, and neuro protection.

Common side effects include gastrointestinal (GI) distress, tremor, sedation, hair loss, increased appetite and weight gain. Hepatic failure, pancreatitis, and hyperammonemic encephalopathy are rare serious side effects associated with use of valproate. Routine blood level monitoring is not necessary. There is an increased risk of fetal abnormalities if valproateis taken in pregnancy.

Valpraote concentrations are known to be increased with concurrent use of benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDS) such as spirin, cemitidine and erythrpmycin. Its level decrease when administrated with phenobarbitone, phenytoin and carbamazepine.

Keywords: Valproate; Pharmacokinetics; Pharmacodynamics; Side effects; Drug interaction

Introduction

Valproate (VPA) is a medication primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches [1]. Valproate is effective in rapid cycling and mixed episode bipolar disorder than lithium [2,3]. It also has superior efficacy than lithium in treating schizoaffective disorders and augmentation therapy for schizophrenic patients not adequately responded to antipsychotic medications [3-7]. It is useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures. It can be given intravenously or by mouth. Long acting formulations exist [2].

The Depakote form of valproic acid is approved for the acute phase of bipolar disorder. It is also commonly used on a long-term basis, although its prophylactic effects have not been as well established. Valproate is used as a first-line treatment for bipolar disorders especially for patients with rapid cycling and mixed episodes, as well as in combination with lithium for patient's refractory to lithium monotherapy. Oral loading can lead to rapid stabilization, and plasma levels must be monitored to keep drug levels within the therapeutic range [6-9].

Common side effects include gastrointestinal (GI) distress, tremor, sedation, hair loss, increased appetite, and weight gain. Hepatic failure, pancreatitis and hyperammonemic encephalopathy are rare serious side effects associated with use of valproate. It is known to cause serious abnormalities in the baby if taken during pregnancy. Because of this it is not typically recommended in women of childbearing age. Menstrual disturbances, polycystic ovaries, hyperandrogenism, obesity, and insulin resistance may also be associated with valproic acid therapy [2,4,6]. Overdose with valproate can result in heart block, coma, and death. Haemodialysis may be useful in clearing the drug rapidly, and naloxone may reverse the central nervous system depressant effects [10].

Mechanism of Action of Valproate (Pharmacodynamics)

The specific biochemical mechanism of valproate action in stabilizing mood is unknown. Its anticonvulsant effects are rapid in onset, while antimanic and antidepressant effects are slower in onset which require chronic administration. It exerts effects by modulation of dopaminergic and serotonergic neurotransmitters, antagonism of glutamate NMDA activity , enhancement of brain γ-aminobutyric acid (GABA) synthesis and degradation, and blockage of voltage sensitive Na+ channels, alter intracellular signaling through actions on second messenger systems secondary messenger systems, modulate extra hypothalamic neuropeptides. In additions it has neuroprotective effects which increase the levels of neuroprotective proteins through suppression of an up regulated brain arachidonic acid (AA) cascade, which can cause cell damage and behavioral changes [11,12].

GABA neurotransmission: GABA is an inhibitory neurotransmitter that plays an important role in regulating dopamine and glutamate neurotransmission. It was found that patients with bipolar disorder had lower GABA levels, which results in excitotoxicity and can cause apoptosis(cell loss) [11,12].

In general the mechanism of action of valproate is complex and still the subject of uncertainty. The drug appears to act by enhancing GABAergic function. Thus it increases GABA release, inhibits catabolism and increases the density of GABA-B receptors in the brain. There is also evidence that it increases the sensitivity of GABA

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receptors to the action of the inhibitory transmitter. Other actions that may contribute to its therapeutic effects include a decrease in dopamine turnover, a decrease in the activity of the NMDA-glutamate receptors and also a decrease in the concentration of somatostatin in the CSF. Valpraote produce its manic effect through this GABAergic effect where sodium valproate raises cerebral and cerebellar levels of the inhibitory synaptic neurotransmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase, succinate-semialdehyde dehydrogenase and by inhibiting the re-uptake of GABA by neuronal cells [11,12].

Reduction in phosphatidylinositol: The other mechanism where valproate boost its effect is through protection against a seizure-induced reduction in phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [13].

Histone deacetylase-inhibiting effect: Valproate also has histone deacetylase-inhibiting effects where valpraote shows it neuropretive effects. This neuroprotective effects which increase the levels of neuroprotective proteins through suppression of an up regulated brain arachidonic acid (AA) cascade, which can cause cell damage and behavioral changes. Intermediate molecules mediating these effects include Vascular endothelial growth factor (VEGF, neuroprotective brain-derived neurotrophic factor (BDNF) and Glial-derived neurotrophic factor (GDNF) [14,15].

Effects on androgen and progesterone receptors: Valproate has been found to be an antagonist of the androgen and progesterone receptors, and hence a non-steroidal antiandrogen and antiprogestogen, at concentrations much lower than therapeutic serum levels. It was concluded that these actions are likely to be involved in the reproductive endocrine disturbances seen with valproic acid treatment [16].

Glutamate neurotransmission; Glutamate is the universal excitatory neurotransmitter. The mechanism of action of valproate on glutamate neurotransmitter is less well-studied. It has a glutamate antagonist activity (reduces NMD A-glutamate activity). Valproate interferes with neurotransmission by the excitatory neurotransmitter glutamate, in particular reducing its release [11].

Effects on voltage-gated sodium channels: like carbamazepine valproate also produce its effects by blockade of voltage-gated sodium channels. By doing this valproate like carbamazepine decreases influx of sodium ion and increases efflux of potassium ion [11].

Dopaminergic and serotonergic transmission: Dopamine and serotonin are major neurotransmitters involved in the patho-physiologic mechanism of bipolar disorders. Valproate produces its mood stabilizing effects by modulation of dopaminergic and serotonergic transmission [11].

Pharmacokinetics of Valproate

Valproate is highly protein bound, primarily to albumin and it is generally thought that, at serum levels less than 45 to 50 μg/mL, these binding sites are unsaturated; at higher serum levels, these binding sites become saturated, with the unbound valproate level increasing or resulting in more unbound drug being available. This enhances the metabolism of the drug and lowers the serum concentration. Valproate is rapidly absorbed; with peak plasma concentrations obtained 3 to 4 h after oral administration. The plasma half-life of valproate is 10 to 16 h. The unbound portion of valproate is considered to be pharmacologically active and can cross the blood–brain barrier. Comparatively, valproate has a higher degree of plasma protein binding and, when used in combination with other psychotropic agents, can increase free levels of other drugs (i.e., lamotrigine [Lamictal] and carbamazepine). Valproate is metabolized primarily by hepatic glucuronidation and mitochondrial β-oxidation. When dosed in combination with drugs that induce cytochrome P450 enzymes (i.e., carbamazepine [Tegretol]), the half-life is shorter. Decreased protein binding (higher serum levels) is seen in the elderly and in patients with hepatic and renal disease. These patients are at greater risk for toxicity [17,18].

Pre Valproate Work Up and Monitoring

Before starting valpraote treatments other causes of mood disorder or manic symptoms, including medical disorders, medications and substances of abuse, should be excluded. Screening laboratory exams should include liver function tests and a CBC. In females of childbearing age, pregnancy should be excluded due to valproate use during the first trimester is associated with teratogenic effect (especially neural tube defect such as spinal bafidat). Start folic acid supplement in women (pregnant) who are sodium valproate. Steady state achieved after 4-5 days - check 12 h after last dose and repeat CBC and LFTs. Goal: target level is between 50-125 mg/L [7-9,18].

Predictors of Good Valproate Response

Factors predicting positive response to valproate includes Prior history of good response or family member with good response, mixed mania and depression is followed by Mania [7-9,18] (Table 1).

Summary of predictors for good valproate response:

1) Past history of good valproate response (personal or family)
2) Rapid cycling bipolar disorder (common in females than males)
3) Irritable mania
4) Comorbid substance use disorders
5) Sequence: Depression – Mania - Euthymia
6) Severe mania (with psychosis)
7) Mixed mania
8) Secondary mania

Initial Monitoring	1) Liver function tests (LFTs):
	Use of valproate associated may severe liver damage especially after 6 month.
	Increase liver enzymes may be seen and are usually transient or respond to a reduction in dose.
	2) CBC
	3) Weight and Height (Use of valproate associated with weight gain or obesity)
Six months after starting	1) CBC
	2) LFTs
	3) Weight and height if patient gains weight rapidly (To rule out weight gain or obesity related to sodium use
Routine Monitoring	Routine blood level monitoring is not necessary
Additional Monitoring	1) Valproate level
	If inadequate response obtained or evidence of poor adherence or toxicity. Trough levels of 50-100 mg/L are associated with therapeutic response in bipolar disorder.
	2) CBC
	Indicates the need for a CBC with bleeding time and coagulation tests of there are bruising or bleeding.

Table 1: Summary of pre valproate work up nand monitoring.

9) Comorbid anxiety and panic attack

10) Comorbid migraine headache

Side Effects of Valproate

Common side effects of valproate

Common side effects include gastrointestinal (GI) distress, tremor, sedation, hair loss, increased appetite and weight gain. Generally, most of the common side effects are dose related and can often be minimized by dose reduction, dose consolidation, or adjunctive pharmacotherapy [18-29].

Valproate use is also associated with risk of polycystic ovarian syndrome, however relationship between valproate, polycystic ovaries, and polycystic ovarian syndrome (menstrual irregularity and clinical evidence of hyperandrogenism) remains controversial because patients with epilepsy and obesity appear to be at increased risk for the syndrome [18,30].

Rare dangerous side effects of valproate

Hepatic failure, pancreatitis, and hyperammonemic encephalopathy are rare serious side effects associated with use of valproate. It is important to obtain baseline hepatic function tests before valproate treatment. However, baseline or serial laboratory monitoring does not necessarily predict severe hepatotoxicity or pancreatitis. Close clinical observation is far superior to routine clinical monitoring in this regard. Additional warnings include sedation in the elderly and thrombocytopenia [18-21] (Table 2).

Pregnancy and Valproate

Use of valpraote during pregnancy especially associated with teratogenic effects. The teartogenic risk ranges 1 to 4 percent (neural tube defects, such as spina bifida). Preconceptual education and folate-vitamin b complex supplementation for all for pregnant women is necessary [18,31-35].

Common side effects	GI distress
	Sedation
	Liver transaminase elevation
	Tremor
	Hair loss
	Weight gain-increased appetite
	Thrombocitopenia (elders)
	Teratogenic: neural tube, cranio-facial
Less common side effects	Neutropenia
	Coagulopathies, decrease in platelet Function
	cranofacial abnormalities
	Amenorrhea, policystic ovary
	Hypothyroidism
	Hypocortisolemia
Rare Dangerous side effects	1) Idiosincratic Heptic Failure
	a. lethargy, anorexia, N/V, jaundice , bleed, edema
	b. Risk: <2 years., many anticonvulsants (poly pharmacy), Developmental delay
	c. Remote risk in >10 years of psychiatric patients
	2) Acute Hemorrhagic Pancreatitis
	3) Bone Marrow Supression
Teratogenicity	Neural tube defect in 1-4% of patients especially use in first trimester
	Preconception education and folate-vitamin B complex supplementation for all for pregnant women is necessary

Table 2: Summary of side effects of valproate.

Overdose and Toxicity of Valproate

Overdose with valproate can result in heart block, coma, and death. Haemodialysis may be useful in clearing the drug rapidly, and naloxone may reverse the central nervous system depressant effects. In general, serum or plasma valproic acid concentrations are in a range of 20–100 mg/l during controlled therapy, but may reach 150–1500 mg/l following acute intoxications. Supportive therapy should be given to all patients experiencing an overdose and urine output should be monitored. Supplemental L-carnitine is indicated in patients having an acute overdose and also prophylactically in high risk patients. Acetyl-L-carnitine lowers hyperammonemia less markedly than L-carnitine [36-41].

Drug Interactions

The primary pharmacokinetic liability of valproate is related to its plasma protein binding capacity and the inhibition of other drugs metabolized by the liver. Valpraote concentrations are known to be increased with concurrent use of benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDS) such as spirin, cemitidine and erythrpmycin. . Its level decrease when administrated with phenobarbitone, phenytoin and carbamazepine). In contrast valpraote reduces clearance of other antiepileptics (including carbamazepine, lamotrigine, phenytoin and phenobarbitone). Valpraote may also potentiate the CNS depressant effects of alcohol. The common drug interactions are indicated below [1-5,18,42,43].

Anticonvulsant Interactions

1. Valproate inhibits phenobarbital metabolism and reduces clearance. Phenobarbital causes non-P450 enzyme induction and lowers valproate levels.
2. Valproate inhibits phenytoin metabolism and reduces clearance Phenytoin causes non-P450 enzyme induction and lowers valproate levels.
3. Carbamazepine causes non-P450 enzyme induction and lowers valproate levels.
4. Valproate inhibits the metabolism of lamotrigine and ethosuximide and decrease clearance.
5. The combination of valproate and clonazepam has been reported to cause absence seizures

Other Interactions

1. Valproate increases the free concentration of diazepam by plasma protein binding site displacement and also has been shown to decrease the serum level of a diazepam metabolite N-desmethyl diazepam.
2. Valproate inhibits the metabolism of amitriptyline and nortriptyline, resulting in increased levels.
3. Valproate inhibits the metabolism of AZT (Zidovudine) increase serum levels and lead to toxicity
4. Valproate can displace warfarin from protein binding and increase warfarin concentration and prolong bleeding time.
5. Rifampin will increase valproate clearance and result in decreased serum concentrations.

6. Aspirin inhibit the metabolism of valproate with resultant increases in serum levels and increased potential for toxicity. May also interfere with valproate's metabolism
7. Benzodiazepines: Valproate inhibits the metabolism of bezodiazepines, resulting in increased levels cause CNS depression.
8. Cimetidine: Inhibits valproate's metabolism in the liver, leading to increased valproate concentrations.
9. Erythromycin: inhibits valproate's metabolism in the liver, leading to increased valproate concentrations

Conclusion

Valproate is it is the first line drug for bipolar patients with presence rapid cycling, irritable mania, bipolar disorder with comorbid substance use disorders, severe mania with psychosis, mixed mania and secondary mania. It is a mood stabilizer which is approved for use in acute and maintenance mania.

Understanding of Mechanism of Action of Valproate (pharmacodynamics), pharmacokinetics, common side effects and monitoring schemes is vital for prescribers and other professionals.

Concomitant use of this medication with Valproate should be carried out with caution and adequate supervision. In addition, concomitant use of other drugs metabolized by same enzyme may predispose individual for side effects or reduce the effectiveness of the drugs. Prescribers need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and its importance and potential drug interactions. Prescribing advice should highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.

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