Review on Sodium Valproate: Mechanism, Pharmacokinetics, Adverse Effects

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Abstract- Valproate (valproic acid, VPA, sodium valproate, and valproate semi sodium forms) are medications primarily used to treat epilepsy and bipolar disorder and prevent migraine headaches. They are useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures. They can be given intravenously or by mouth, and the tablet forms exist in both long- and short-acting formulations. Valproate's precise mechanism of action is unclear. Proposed mechanisms include affecting GABA levels, blocking voltage-gated sodium channels, inhibiting histone deacetylases, and increasing LEF1. Valproic acid is a branched short-chain fatty acid (SCFA), a derivative of valeric acid.

Keywords: fetal, valproate, Pharmacokinetics, toxicity

INTRODUCTION

Valproate was first made in 1881 and came into medical use in 1962. It is on the World Health Organization's List of Essential Medicines and is available as a generic medication. In 2021, it was the 155th most commonly prescribed medication in the United States, with more than 3 million prescriptions. Valproic acid was first synthesized in 1882 by Beverly S. Burton as an analogue of valeric acid, found naturally in valerian. Valproic acid is a carboxylic acid, a clear liquid at room temperature. For many decades, its only use was in laboratories as a "metabolically inert" solvent for organic compounds. In 1962, the French researcher Pierre Eymard serendipitously discovered the anticonvulsant properties of valproic acid while using it as a vehicle for a number of other compounds that were being screened for antiseizure activity. He found it prevented pentylenetetrazol-induced convulsions in laboratory rats. It was approved as an antiepileptic drug in 1967 in France and has become the most widely prescribed antiepileptic drug worldwide. Valproic acid has also been used for migraine prophylaxis and bipolar disorder. Valproate has a broad spectrum of anticonvulsant activity, although it is primarily used as a first-line treatment for tonic–clonic seizures, absence seizures and myoclonic seizures and as a second-line treatment for partial seizures and infantile spasms. It has also been successfully given intravenously to treat status epilepticus.

In the US, valproic acid is an anti-epileptic drug indicated for the treatment of manic episodes associated with bipolar disorder; monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in people with multiple seizure types that include absence seizures. Based upon five case reports, valproic acid may have efficacy in controlling the symptoms of the dopamine dysregulation syndrome that arise from the treatment of Parkinson's disease with levodopa. Valproate is also used to prevent migraine headaches. The medication has been tested in the treatment of AIDS and cancer, owing to its histone-deacetylase-inhibiting effects. It has cardioprotective, kidney protective, anti-inflammatory, and antimicrobial effects. Valproate exists in two main molecular variants: sodium valproate and valproic acid without sodium (often implied by simply valproate). A mixture between these two is termed semi sodium valproate. It is unclear whether there is any difference in efficacy between these variants, except from the fact that about 10% more mass of sodium valproate is needed than valproic acid without sodium to compensate for the sodium itself. Valproate is a negative ion. The conjugate acid of valproate is

valproic acid (VPA). Valproic acid is fully ionized into valproate at the physiologic pH of the human body, and valproate is the active form of the drug. Sodium valproate is the sodium salt of valproic acid. Divalproex sodium is a coordination complex composed of equal parts of valproic acid and sodium valproate. Valproate inhibits CYP2C9, glucuronyl transferase, and epoxide hydrolase and is highly protein bound and hence may interact with drugs that are substrates for any of these enzymes or are highly protein bound themselves. Valproate was evaluated in the treatment of seizures in infants aged 1 to 36 months. In a randomized control trial, valproate alone was found to show poorer outcomes for infants than valproate plus levetiracetam in terms of reduction of seizures, freedom from seizures, daily living ability, quality of life, and cognitive abilities. Valproate causes birth defects; exposure during pregnancy is associated with about three times as many major abnormalities as usual, mainly spina bifida with the risks being related to the strength of medication used and use of more than one drug. "Fetal valproate syndrome" (FVS) has been used to refer to the effects of valproate exposure in utero. However, similar to the discussion about the adverse effect of exposure to alcohol in utero ("fetal alcohol spectrum disorder"), a 2019 study proposed the term "Fetal Valproate Spectrum Disorder" (FVSD) because valproate exposure can lead to a wide range of possible presentations, which can be influenced by various factors (including dosage and timing of exposure). The dysmorphic features associated with VPA exposure can be subtle and age-dependent, making it challenging to designate individuals as having the characteristic dysmorphism or not, especially for those with limited expertise in the area. While the presence of typical facial dysmorphism is suggestive of the condition, it is not required for diagnosis. This change in terminology to FVSD would benefit individuals affected by the neurodevelopmental effects of VPA exposure without significant malformations, since they can experience impairments in their everyday functioning similar to those with classical FVS. Characteristics of valproate syndrome may include facial features that tend to evolve with age, including a triangle-shaped forehead, tall forehead with bifrontal narrowing, epicanthic folds, medial deficiency of eyebrows, flat nasal bridge, broad nasal root, anteverted nares, shallow philtrum, long upper lip and thin vermillion borders, thick lower lip and small downturned mouth. While developmental delay is usually associated with altered physical characteristics (dysmorphic features), this is not always the case.

Children of mothers taking valproate during pregnancy are at risk for lower IQs. Maternal valproate use during pregnancy increased the probability of autism in the offspring compared to mothers not taking valproate from 1.5% to 4.4%. A 2005 study found rates of autism among children exposed to sodium valproate before birth in the cohort studied were 8.9%. The normal incidence for autism in the general population in 2018 was estimated at 1 in 44 (2.3%). An updated March 2023 report estimates the number increased to 1 in 36 in 2020 (approximately 4% of boys and 1% of girls). A 2009 study found that the 3-year-old children of pregnant women taking valproate had an IQ nine points lower than that of a well-matched control group. However, further research in older children and adults is needed. Sodium valproate has been associated with paroxysmal tonic upgazed of childhood, also known as Ouvrier–Billson syndrome, from childhood or fetal exposure. This condition resolved after discontinuing valproate therapy. Women who intend to become pregnant should switch to a different medication if possible or decrease their dose of valproate. Women who become pregnant while taking valproate should be warned that it causes birth defects and cognitive impairment in the newborn, especially at high doses (although valproate is sometimes the only drug that can control seizures, and seizures in pregnancy could have worse outcomes for the fetus than exposure to valproate). Studies have shown that taking folic acid supplements can reduce the risk of congenital neural tube defects. The use of valproate for migraine or bipolar disorder during pregnancy is contraindicated in the European Union and the United States, and the medicines are not recommended for epilepsy during pregnancy unless there is no other effective treatment available

Fig 1: Sodium Valproate tablet

Mechanism of Action

The mechanism of action of valproate is not fully understood, traditionally, its anticonvulsant effect has been attributed to the blockade of voltage-gated sodium channels and increased brain levels of the inhibitory synaptic neurotransmitter gamma-aminobutyric acid (GABA). The GABAergic effect is also believed to contribute towards the anti-manic properties of valproate. In animals, sodium valproate raises cerebral and cerebellar levels of 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. Prevention of neurotransmitter-induced hyperexcitability of nerve cells via Kv7.2 channel and AKAP5 may also contribute to its mechanism. Valproate has been shown to protect against a seizure-induced reduction in phosphatidylinositol (3,4,5)-trisphosphate (PIP3) as a potential therapeutic mechanism. Valproate is a Histone deacetylase inhibitor. By inhibition of histone deacetylase, it promotes more transcriptionally active chromatin structures that are it exerts an epigenetic effect. This has been proven in mice: Valproic acid induced histone hyperacetylation had brain function effects on the next generation of mice through changes in sperm DNA methylation. Intermediate molecules include VEGF, BDNF, and GDNF.

Toxicity:

Excessive amounts of valproic acid can result in somnolence, tremor, stupor, respiratory depression, coma, metabolic acidosis, and death. 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 poisoning. Monitoring of the serum level is often accomplished using commercial immunoassay techniques, although some laboratories employ gas or liquid chromatography. In contrast to other antiepileptic drugs, at present there is little favourable evidence for salivary therapeutic drug monitoring. Salivary levels of valproic acid correlate poorly with serum levels, partly due to valproate's weak acid property (p*K*a of 4.9). In severe intoxication, hemoperfusion or hemofiltration can be an effective means of hastening elimination of the drug from the body. Supportive therapy should be given to all patients experiencing an overdose and urine output should be monitored.

Contraindications include: -

- Pre-existing acute or chronic liver dysfunction or family history of severe liver inflammation (hepatitis), particularly medicine related.
- Known hypersensitivity to valproate or any of the ingredients used in the preparation
- Urea cycle disorders
- Hepatic porphyria
- Hepatotoxicity
- Mitochondrial disease
- Pancreatitis
- Porphyria
- Pregnancy (except when no other treatments are available for the treatment of epilepsy)

Most common adverse effects include:[3]

- Nausea (22%)
- Drowsiness (19%)
- Dizziness (12%)
- Vomiting (12%)
- Weakness (10%)

Serious adverse effects include:[3]

Valproic acid has a black box warning for hepatotoxicity, pancreatitis, and fetal abnormalities. There is evidence that valproic acid may cause premature growth plate ossification in children and adolescents, resulting in decreased

height. Valproic acid can also cause mydriasis, a dilation of the pupils. There is evidence that shows valproic acid may increase the chance of polycystic ovary syndrome (PCOS) in women with epilepsy or bipolar disorder. Studies have shown this risk of PCOS is higher in women with epilepsy compared to those with bipolar disorder. Weight gain is also possible.

- Bleeding
- Low blood platelets
- Encephalopathy
- Suicidal behavior and thoughts
- Low body temperature

Structure feature of Sodium Valproate

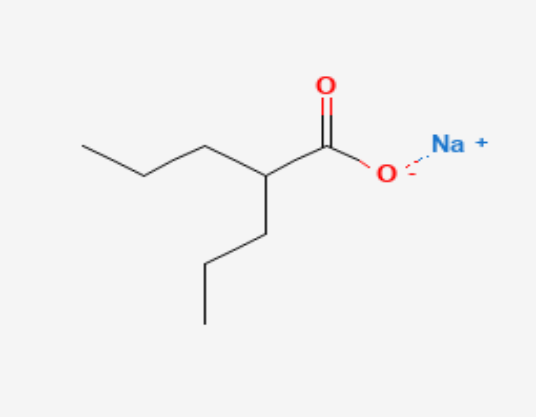

Fig 2: Structure feature of sodium valproate

IUPAC NAME:
Molecular formula: $C_8H_{16}O_2$
Molar Mass: 144.214 g·mol^{-1}
Metabolism: Liver—glucuronide conjugation 30–50%, mitochondrial β-oxidation over 40%
Bioavailability: Rapid Absorption
Excretion: Urine (30–50%)
Protein Binding: 80–90%
Elimination Half Life: 9–16 hour

Pharmacokinetics:
Taken by mouth, valproate is rapidly and virtually completely absorbed from the gut. When in the bloodstream, 80–90% of the substance is bound to plasma proteins, mainly albumin. Protein binding is saturable: it decreases with increasing valproate concentration, low albumin concentrations, the patient's age, additional use of other drugs such as aspirin, as well as liver and kidney impairment. Concentrations in the cerebrospinal fluid and in breast milk are 1 to 10% of blood plasma concentrations.
The vast majority of valproate metabolism occurs in the liver. Valproate is known to be metabolized by the cytochrome P450 enzymes CYP2A6, CYP2B6, CYP2C9, and CYP3A5. It is also known to be metabolized by the UDP-glucuronosyltransferase enzymes UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15. Some of the known metabolites of valproate by these enzymes and uncharacterized enzymes include: -

- via glucuronidation (30–50%): valproic acid β-O-glucuronide
- via beta oxidation (>40%): 2*E*-ene-valproic acid, 2*Z*-ene-valproic acid, 3-hydroxyvalproic acid, 3-oxovalproic acid
- via omega oxidation: 5-hydroxyvalproic acid, 2-propyl-glutaric acid
- some others: 3*E*-ene-valproic acid, 3*Z*-ene-valproic acid, 4-ene-valproic acid, 4-hydroxyvalproic acid

All in all, over 20 metabolites are known.

Brand names of valproic acid

- Absenor (Orion Corporation Finland)
- Convulex (G.L. Pharma GmbH Austria)
- Depakene (Abbott Laboratories in US and Canada)
- Depakin (Sanofi S.R.L. Italy)[127]
- Depakine (Sanofi Aventis France)
- Depakine (Sanofi Synthelabo Romania)
- Depalept (Sanofi Aventis Israel)
- Deprakine (Sanofi Aventis Finland)
- Encorate (Sun Pharmaceuticals India)
- Epival (Abbott Laboratories US and Canada)
- Epilim (Sanofi Synthelabo Australia and South Africa)
- Stavzor (Noven Pharmaceuticals Inc.)
- Valcote (Abbott Laboratories Argentina)
- Valpakine (Sanofi Aventis Brazil)
- Orfiril (Desitin Arzneimittel GmbH Norway)

Endocrine actions
Valproic acid has been found to be an antagonist of the androgen and progesterone receptors, and hence as a nonsteroidal antiandrogen and antiprogestogen, at concentrations much lower than therapeutic serum levels. In addition, the drug has been identified as a

potent aromatase inhibitor, and suppresses estrogen concentrations. These actions are likely to be involved in the reproductive endocrine disturbances seen with valproic acid treatment. Valproic acid has been found to directly stimulate androgen biosynthesis in the gonads via inhibition of histone deacetylases and has been associated with hyperandrogenism in women and increased 4-androstenedione levels in men. High rates of polycystic ovary syndrome and menstrual disorders have also been observed in women treated with valproic acid

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