Valproic acid and sodium valproate

Valproic acid (active part of chemical)
CAS: 99-66-1
MF: $C_8H_{16}O_2$
MW: 144.21
Log Kow = 2.75
Solubility: Very slightly soluble in water (1.27 mg/ml). Soluble in most organic solvents including methanol, chloroform, and ether [1].

Sodium valproate
CAS: 1069-66-5
MF: $C_8H_{15}O_2Na$
MW: 166.19
Solubility: In water 50 mg/ml [2].

Major uses

Valproic acid is an anticonvulsant agent approved as monotherapy or adjunctive therapy for the prophylactic treatment of complex partial seizures. It is also used for treatment of mania associated with bipolar affective disorder, and for prophylaxis of migraine headaches. An unapproved use of valproic acid includes treatment of neuropathic pain Sodium valproate is also used as an anticonvulsant agent [3].

Human toxicity

Mild overdose of valproic acid can cause somnolence, confusion, gastrointestinal upset (mainly vomiting) and tachycardia. With severe overdose, coma, hypotension, respiratory depression, aspiration, tachycardia, metabolic acidosis and cardiopulmonary arrest may develop. There is little correlation between the CNS effects (depth coma and seizures) and plasma valproate levels. Adverse effects of chronic exposure to valproic acid include hepatotoxicity, pancreatitis, bone marrow suppression and gastrointestinal upset. Sodium valproate causes similar effects as valproic acid.

Lethal symptoms: Coma, respiratory and heart arrest, and multiorgan failure.

Therapeutic dose: 10 to 15 mg/kg/day, initially, given orally in divided doses from once daily to three times daily. The maximum daily recommended dose is 60 mg/kg [3].

Drowsiness was reported in 2 patients ingesting 20 g and 25 g, respectively. Based on these findings, the authors concluded that doses less than 400 mg/kg (valproate only) were unlikely to cause severe toxicity [3]. Severe toxicity is associated with ingestion of 19 to 45 g in adults [1]. Lethal dose is 55 g [4].

Hepatotoxicity has been noted in 11 patients with plasma valproic acid concentrations of 52-148 mg/l (reviewed in [5]). Concentrations of valproic acid varied between 360 and 2725 mg/l in 5 lethal acute poisoning cases (see Table 2a in AcuBase: Lethal acute poisoning (single dose): Clinical observations (time related)).

Kinetic data

Absorption of therapeutic doses of valproic acid is reported to be rapid and complete [3]. The absolute bioavailability of sodium valproate is nearly 100%

Volume of distribution: The apparent volume of distribution of sodium valproate is 0.13 to 0.23 l/kg [3] and of valproic acid is 0.1-0.5 l/kg [5, 6].

Distribution: Valproic acid is accumulated in the kidney after an overdose [3]. Observed brain concentrations of valproic acid have been reported to range from 6.8% to 27.8% of total plasma concentrations. In overdose, elevated cerebrospinal fluid valproic acid concentrations occur due to saturated plasma protein binding sites and higher percentage of circulating free drug [3].

The plasma half-life: During elimination, the drug follows first-order kinetics (6). The half-life following single therapeutic dose has ranged from 7 to 21.5 h [1, 3]. The half-life in patients receiving chronic doses of valproic acid usually ranges from 10 to 14 h. The serum half-life appears to be prolonged in the overdose situation and may be from 30 h up to 4 days [3, 4, 6].

Time to peak: Following therapeutic doses, peak plasma levels occur 1 to 4 h after ingestion [3, 6]. Following overdoses, profound delays to peak plasma concentrations may occur (up to 18h). The mean time to peak serum concentration was reported to be 7.4 h [1, 3, 6].

Protein binding: Valproic acid is 88% to 91% protein bound in healthy patients [3] at serum concentrations up to 50 µg/ml. Following a massive overdose (50-100 µg/ml), saturated protein binding results in increased

fraction of unbound valproic acid. In one overdose case, initial plasma protein binding was reported to be 32% [1, 3].

Metabolism and excretion
Valproic acid (VPA) appears to be rapidly metabolized in the liver to glucuronide conjugates which are subsequently excreted in the urine. The glucuronidation occurs in the endoplasmic reticulum. Nine metabolites have been isolated. β-oxidation of valproic acid occurs in mitochondria and peroxisomes. The principle β-oxidation products are 2-propyl-2-pentenoic acid (2-en-VPA), 3-hydroxy-2-propylpentanoic acid (3-OH-VPA), and 3-oxo-2-propylpentanoic acid (3-keto-VPA). Cytosolic ω-oxidation (14%) and ω_1-oxidation (16%) pathways provide only minor contributions. ω-oxidation products include 5-hydroxy-2-propylpentanoic acid (5-OH-VPA), 2-polyglutaric acid (PGA), and 2-proyl-4-pentenoic acid (4-en-VPA), while ω_1-oxidation products include 4-hydroxy-2-propylpentanoic acid (4-OH-VPA), 4-oxo-2-propyloentanoic acid (4-keto-VPA), and 2-propyl-3-pentenoic acid (3-en-VPA) [6].

Excretion: Up to 86% of a labeled dose of valproic acid is eliminated in urine within 24 h, but only 1-4% of the dose is excreted unchanged [5]. Plasma clearance was reported to 12.7 ml/min in one study [3].

Metabolites more toxic than valproic acid: 5-OH-VPA, 4-OH-VPA and 4-en-VPA are postulated to be hepatotoxic metabolites of valproic acid [3].

Toxicological mechanism
It has been suggested that 2-en-valproic acid metabolite may be at least partially responsible for neurological toxicity.

Pharmacological mechanisms
Valproic acid (sometimes formulated as sodium valproate) is structurally unrelated to other anticonvulsant agents. The mechanism of action is currently unknown. However, it is postulated to interact with the brain gamma-aminobutyric acid (GABA), possibly increasing brain concentrations of this neurotransmitter. Valproic acid may also inhibit the reuptake of GABA into the glia and nerve endings [1, 3].

Target organs*:* CNS, cardiovascular system, liver

References

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