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## What are the effects of taking 300 pills of sodium valproate? - case report

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### ABSTRACT

INTRODUCTION: Sodium valproate is one of the most important antiepileptic drugs. It can be effective as a preventive treatment for migraine, it has also found use in the maintenance treatment of bipolar disorder and acute mania, it is sometimes used in the treatment of chronic

neuropathic pain and fibromyalgia, in the treatment of schizophrenia borderline personality disorder and acquired brain injury, this drug is used off-label. Its overdose can be fatal.

**MATERIALS AND METHOD:** Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on sodium valproate treatment, its toxicity, side effects and pharmacokinetics using PubMed.

**CASE REPORT:** A 57-year-old patient with a history of depressive disorders was admitted to the Clinical Department of Toxicology and Cardiology in Lublin for intentional intoxication with the drug Absenor (sodium valproate). The patient had taken 3 packages of Absenor 500 mg (300 tablets in total) for suicidal purposes. The determined concentration of valproic acid was 841 µg/ml, and the patient's condition was very severe. Despite the treatment administered-multiple attempts at gastric lavage, administration of activated charcoal, performance of hemodialysis procedures, administration of infusion of catecholamines, the patient died on the fifth day of hospitalization.

**CONCLUSION:** An overdose of sodium valproate can be fatal. Keep this in mind when ordering this drug for patients with a positive history of suicide attempts.

**KEY WORDS:** drug overdose; sodium valproate; sodium valproate overdose; sodium valproate poisoning; suicide

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## INTRODUKTION

Sodium valproate was first synthesized in 1882 as a derivative of valerianic acid. [1] It was introduced in continental Europe in 1967, while in 1978 it was approved by the Food and Drug Administration for the treatment of epilepsy. [2, 3] It is one of the most important antiepileptic drugs and is an effective agent in the control of absence seizures, myoclonic, tonic-clonic and partial-acting seizures in both generalized and partial-acting seizures in adults and children. [4] Valproate is often a first-line drug of first choice alone or in combination with other antiepileptic drugs in virtually all types of seizures and epilepsies. [1] It can be effective as a preventive treatment for migraine in children and adolescents as well as adults. [5, 6] A study showed that the addition of magnesium to sodium valproate therapy can enhance the anti-migraine effect and reduce the required dose of valproate for migraine prophylaxis. [7] In addition, sodium valproate has also found use in the maintenance treatment of bipolar disorder

and acute mania in monotherapy or combination treatment. [8] It is sometimes used to treat chronic neuropathic pain and fibromyalgia, although it is not licensed for this use. However, the American Academy of Neurology (AAN 2011) guideline on the pharmacologic and nonpharmacologic treatment of painful diabetic neuropathy (PDN) recommends considering sodium valproate for the treatment of PDN. [9] Valproate may modify neurogenic meningitis through a GABA-dependent mechanism. [10] In the treatment of schizophrenia borderline personality disorder and acquired brain injury, this drug is used off-label. [8, 11]

No single mechanism of action for sodium valproate fully accounts for its various clinical indications and broad spectrum of efficacy. [1] It has effects on dopamine, enhances gamma-aminobutyric acid (GABA) receptors through activation of gamma-aminobutyric acid (GABA)-sensitive chloride channels and inhibition of histone deacetylase, and inhibits NMDA-induced neuroexcitatory signals. [7, 8,10] The main component of sodium valproate is valproic acid (VPA), which is a branched short-chain fatty acid. [12] Regardless of which oral form of sodium valproate is taken, it is rapidly absorbed, and peak serum concentrations are reached within 1 to 3 h. [4] All oral forms are highly bioavailable and extended-release formulations are excellent to minimize fluctuations in serum drug concentration. [1] At therapeutic plasma concentrations, ~ 94% of valproate is bound to plasma proteins such as albumin. The proportion of free valproate increases as the total valproate concentration increases. [8] An effective prophylactic dose of sodium valproate ranges from 500 to 1,500 mg/day. [6] Ranges of therapeutic serum VPA concentrations have been estimated at 500- 1000 µg/ml, or 400- 1500 µg/ml. [4] The American Psychiatric suggests a target range for valproate of 50 - 125 µg/ml in mania, in blood drawn immediately before valproate ingestion. [8] It has been noted that concentrations as high as 200 µg/ml can be found in some patients without any adverse effects. [4]

Routine monitoring of valproate concentrations is not recommended unless there are concerns about patient compliance. [8]

VPA is metabolized in the liver. [12] It is then rapidly eliminated via urinary excretion. [4] Half-life is 9 to 18 h, but shorter (5 - 12 h) in patients taking enzyme-inducing drugs such as phenytoin, carbamazepine and barbiturates. [8]

VPA has a wide spectrum of side effects, which are of concern especially with polytherapy, long-term therapy and in certain categories of patients.[1] Side effects are listed in table number 1 (Tab. 1.) [1, 3, 7, 8, 9, 13, 14, 15].

Tab. 1. Side effects of sodium valproate.

<p><b>SIDE EFFECTS OF SODIUM VALPROATE</b> sedation, fatigue, tremor, gastrointestinal symptoms, weight gain, increased appetite, poor appetite, lethargy, nausea, diarrhea, hair loss with curly regrowth, personality change, sleep problem, depression, slow process speed, memory problem, apathy, skin rashes, hemorrhagic pancreatitis, coagulopathies, bone marrow suppression, hepatotoxicity, encephalopathy teratogenicity and impaired neurocognitive function in offspring, dizziness, mood changes, extrapyramidal symptoms, hyperammonemia (causing nausea), hypocarnitinaemia, thrombocytopenia, leucopenia, aplastic anemia fulminant liver failure, elevation of liver, Stevens–Johnson syndrome transaminase and lactate dehydrogenase enzymes, decrease in bone mineral density, hypothermia, hypotension, palpitations, tachycardia, bradycardia</p> <p>In women: polycystic ovarian syndrome, hyperandrogenism</p>
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However, sodium valproate can cause acute pancreatitis, usually in pediatric patients. The exact mechanism of this phenomenon is unknown. In adult patients with chronic renal failure, sodium valproate-induced pancreatitis is caused by the retention of intermediate metabolites in the body. Risk factors for this phenomenon include genetics, age (the younger the patient, the more often), comorbidities, and initial dose and titration rate, diseases. [3]

Sodium valproate can cause dose-independent hepatic hepatotoxicity. [16] 5-10% of patients will have mild elevation of serum aminotransferases and transaminases, without progression to significant liver damage; another 16-80% of patients will develop hyperammonemia, mostly asymptomatic, within the first 6 months of therapy, but a minority of patients may develop encephalopathy, with lethargy, lethargy, and confusion. [17] With mild and asymptomatic liver effects, there is no need to discontinue valproate. [8] In contrast, it is important to remember that VPA can cause potentially fatal liver toxicity, especially in patients with risk factors (young age, polytherapy, and inborn metabolic defects such as mitochondrial disorders). [1] Hepatic toxicity is most common in children under 2 years of age who are treated with a few anticonvulsants (incidence is as high as 1 in 600), while it is very rare in the adult population (incidence is estimated at 1 in 20,000). [8] Children with mitochondrial abnormalities are at increased risk of severe hepatotoxicity, so it is suggested that in some cases screening for certain mitochondrial DNA polymerase gamma mutations should be performed before

valproate is prescribed. [17] The exact mechanism of VPA hepatotoxicity is not clear. There was a study in which, it was shown, that melatonin administration has a protective effect on oxidative damage, inflammation and apoptosis in VPA-induced liver toxicity. [16]

Another very serious effect of sodium valproate therapy can be encephalopathy. The literature reports that this is a rare side effect, usually described in patients with inborn errors of metabolism, but also in patients without known metabolic defects, especially when VPA was combined with topiramate. [1] The cause of valproate-induced encephalopathy secondary to hyperammonemia is multifactorial. Attention is drawn to carnitine deficiency, which results from both acute valproate toxicity and subsequent long-term use of sodium valproate despite normal plasma concentrations, especially when prescribed with other antiepileptic drugs or when concomitant antibiotics are administered. [12] There have been documented cases of successful use of naloxone in valproic acid-induced encephalopathy. [12]

All psychotropic drugs cross the placenta. [13] Valproate has teratogenic effects. [8] Exposure to VPA in women during the first trimester of pregnancy results in defects of major organs, while exposure later in pregnancy, when brain cells are proliferating and migrating, increases the risk of neurodevelopmental events. [4]

Table 2 (Tab. 2.) summarizes the effects of valproate on the fetus and the pregnant woman. [1, 2, 4, 8, 13, 17]

Tab. 2. Summary of the effects of valproate on the fetus and the pregnant woman.

<p>EFFECT OF VALPROATE ON THE FETUS AND CHILD</p>	<ul style="list-style-type: none"> <li>● birth defects (neural tube defects, spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis, genitourinary defects, omphalocele, inguinal hernia, duodenal atresia, scoliosis),</li>   <li>● intra-uterine growth restriction,</li> </ul>
	<p>infant hepatic toxicity and foetal distress during labour,</p> <ul style="list-style-type: none"> <li>● withdrawal symptoms in the baby right after birth (nervousness, irritability, hypotonia, seizures),</li>   <li>● endocrine disorders, hyperbilirubinemia, hepatotoxicity, transient hyperglycemia, afibrinogenemia,</li>   <li>● developmental delays, decreased verbal intelligence and impaired neurocognitive function in the offspring, autism spectrum disorder</li> </ul>

	<ul style="list-style-type: none"> <li>• Fetal valproate syndrome (FVS) develops after exposure to VPA in utero. It includes a characteristic facial appearance (trigonocephaly, high forehead with bipartite constriction, epidermal folds, infraorbital furrow, medial absence of eyebrows, flat nasal ridge, wide nasal root, flat nasal ridge, shallow jaw, long upper lip with thin border, thick lower lip, small and narrowed lips) and neurodevelopmental delay, there are syndromes of limb and digital abnormalities, in particular missing or short radius, NTDs, congenital heart defects, oral clefts, genital abnormalities and</li> </ul>
	<p>limb defects. About 10% of offspring with FVS are small for gestational age, and withdrawal symptoms are commonly observed in the neonatal period.</p>
EFFECT OF VALPROATE ON A WOMAN	<p>Increased hepatic clearance of valproate and increased apparent volume of distribution cause lower maternal levels of the drug</p>

The European Medicines Agency in 2018 issued an official recommendation that valproate should not be used by women during their childbearing years if pregnancy prevention methods are not used systematically; prescribing valproate during pregnancy is considered justified only if epilepsy could not be controlled with other anticonvulsants. [17] To prevent or minimize the harmful effects of VPA, it is recommended that pregnant women take the lowest effective dose,

avoid polytherapy if possible, and increase daily FA intake to 4 - 5 mg initially during the preconceptional period and throughout pregnancy. [4]

Valproate is secreted into breast milk, with a concentration of 1 - 10% of the serum concentration.[8] In contrast, it is suggested to change pharmacotherapy from lithium precisely to breastfeeding sodium valproate. [18]

Significant progress has been made in understanding the hepatotoxicity, teratogenicity and fetotoxicity of sodium valproate which provides opportunities to prevent them and long-term administration of this drug is relatively safe. [17] Because of the possibility of a causal relationship with PCOS, the NICE guideline on bipolar disorder recommends avoiding valproate in women aged < 18 years. [8] However, it should be considered in pediatric and adolescent women as a treatment option for seizures with high morbidity and mortality. [1] Caution should be exercised when using valproate in patients with liver disease, and note that it is contraindicated in patients with urea cycle disorders, a group of rare genetic abnormalities that include ornithine transcarbamylase enzyme deficiency, and patients with acute porphyrias. [8]

## MATERIALS AND METHOD

Patient information was collected from hospital records available in the clinical toxicology department. In addition, we conducted a literature review on sodium valproate treatment, its toxicity, side effects and pharmacokinetics using PubMed.

## CASE REPORT

A 57-year-old patient with a history of depressive disorders was brought from the ED in Łęczna and admitted to the Clinical Department of Toxicology and Cardiology in Lublin for intentional intoxication with the drug Absenor (sodium valproate).

According to the patient's family history, he had taken 3 packages of the drug Absenor 500 mg (300 pills in total) for suicidal purposes. This was the patient's third suicide attempt; previous ones also by taking antiepileptic drugs had occurred 7 and 12 years earlier.

The sodium valproate poisoning occurred several hours before the patient was transported to Lublin. The patient was initially treated and diagnosed at the district hospital; due to lack of improvement after the treatment administered at the district hospital, the patient was referred to a toxicology center. At the ED in Lublin, due to the presence of respiratory failure, the patient was intubated and ventilator therapy was started.



On admission to the ward, the patient was in a very serious general condition, unconscious, intubated, mechanically ventilated, areactive, with a heart rate of 60/min, hypotonia 90/60 mmHg, pinpoint pupils. Laboratory tests showed metabolic acidosis, renal failure, rhabdomyolysis, valproic acid concentration determined was 841 µg/ml. The CT performed described tablet masses in the stomach, so gastric lavage was performed, even though it had been a long time since the poisoning. Multiple attempts at gastric lavage were made, activated charcoal was administered, a central line and a dialysis line were inserted. This was followed by a 6-hour hemodialysis procedure. An infusion of catecholamines was started due to increasing hypotonia. Due to the conglomerate present in the stomach and the possibility of continuous release and absorption of the drug, gastroscopy was performed. Gastroscopy was made, in which the visible mass of tablet clump was removed with a mesh, the stomach was washed out, the contents were aspirated, and there were no signs of fresh bleeding. During the following days of hospitalization, the patient remained in serious condition, on ventilator respiration and infusion of catecholamines. Due to anuria and increasing parameters of multiple organ failure, two more hemodialysis procedures were performed during the stay. Due to the onset of thrombocytopenia, 1 pack of Platelet Cell Concentrate was transfused. On the fifth day of hospitalization, sudden bradycardia and then asystolic cardiac arrest occurred. Resuscitation efforts were undertaken and a return of hemodynamically efficient heart rate was achieved. After some time, another cardiac arrest occurred in the asystole mechanism. Resuscitation efforts were undertaken and again a return of hemodynamically efficient heart action was achieved. Pharmacotherapy was intensified. Another cardiac arrest occurred in the asystole mechanism soon followed. Resuscitation measures were undertaken. In view of the ineffectiveness of the ongoing activities, the patient was pronounced dead.

## DISCUSSION

Sodium valproate has a fairly wide therapeutic window, so accidental overdose is rare. [8] At therapeutic serum concentrations (40 to 100 µg/ml), valproic acid has low toxicity. Acute valproic acid poisoning occurs at serum concentrations above 100 µg/ml. [19] Symptoms of overdose include CNS depression, which can progress to respiratory depression, coma and death. [8] Table 3 (Tab. 3.) shows the symptoms of acute sodium valproate poisoning. [19]

Tab. 3. Symptoms of acute sodium valproate poisoning.

SYMPTOMS OF ACUTE SODIUM VALPROATE POISONING
Symptoms of poisoning include confusion, sedation or coma, muscle weakness, weakened reflexes/areflexes, miosis, respiratory distress, metabolic acidosis, hypoglycemia, cardiovascular disorders, hypotension, circulatory failure/shock.

The sodium in this form of valproate can cause hypernatremia after overdose. [19]

No specific antidote is known for sodium valproate overdose. [19] Depending on the time at which valproate was taken, the form of treatment chosen is. Gastric lavage or activated charcoal is suggested if VPA is suspected to be in the stomach, while hemodialysis is used in severe cases. [8] Hemodialysis is considered depending on the patient's condition and the concentration of the drug (usually with values close to 1000 µg/ml).

If a suicide attempt occurs, always consider the possibility of poisoning after taking several drugs. [19]

The patient admitted after a suicide attempt after taking 3 packs of Absenor 500 mg (300 pills in total). The patient was brought to the toxicology center almost 24 hours after the intoxication. The measured concentration of valproic acid was 841 µg/ml. The patient had a panel of tests for intoxication with additional substances-ethanol, tricyclic antidepressants, carbamazepine, zonisamide, topiramate, lamotrigine, levetiracetam, benzodiazepines, acetaminophen and barbiturates, which showed the absence of these substances in the patient's serum. Thus, we were dealing with poisoning by sodium valproate alone.

The patient represented the typical symptoms of acute sodium valproate poisoning: respiratory distress requiring intubation and assisted breathing, coma, hypotension. He had metabolic acidosis, renal failure, and rhabdomyolysis. These symptoms led to the development of shock and then death. On admission, his serum sodium level was 155.3 mmol/L, and on the second day his level was within the normal range.

All forms of treatment for poisoning with this substance were applied to the patient. At the initial stage, gastric lavage was performed several times. Activated charcoal was then administered and a hemodialysis procedure was performed. Since it was not possible to perform gastroscopy right away at the on-call admission, it was performed the next day and the visible mass of the tablet-valprominate clump was removed with a mesh, the stomach was

rinsed, the contents were aspirated and there were no signs of fresh bleeding. During treatment, the patient's vital functions were monitored and supported all the time.

Despite the treatment administered, the patient's condition deteriorated, and he was on ventilator breathing and infusion of catecholamines. Due to anuria and increasing parameters of multiple organ failure, two more hemodialysis procedures were performed during his stay. Due to the occurrence of thrombocytopenia, 1 pack of Platelet Cell Concentrate was transfused. On the fifth day of hospitalization, the patient died.

Prescribing sodium valproate therapy to a patient with a history of suicide attempts should be very prudent. The doctor should keep in mind that the patient, despite denying the desire, if given a prescription for several months of therapy with this drug, may take it all at once. The solution to such a situation would be to issue the patient with small amounts of this drug, for short-term therapy.

## CONCLUSION

An overdose of sodium valproate can be fatal. Keep this in mind when prescribing this drug to patients with a positive history of suicide attempts. Prescriptions can be prescribed for a shorter duration of therapy to avoid a patient becoming a holder of a large number of packs of sodium valproate, and so potentially minimize the risk of committing a successful suicide attempt.

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