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# CHRONIC VALPORIC ACID TOXICITY IN CHILDREN: OVERVIEW AND MANAGEMENT

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## ABSTRACT

Valproic acid is an anti-epileptic drug used to treat partial and generalized seizures, acute mania, as prophylaxis for bipolar disorder and migraine headaches. The mechanism of action of valproic acid is its ability to potentiate the effect of neurotransmitter Gamma Amino Butyrate (GABA). Valproic acid intoxication may lead to central nervous system depression, encephalopathy, respiratory depression, hypotension, bone marrow depression, acid-base disorders, hyperammonemia, and elevated liver enzymes. Several methods had been suggested to treat valproic acid intoxication, like supportive treatment, naloxone injection, l-carnitine, activated charcoal, and hemofiltration .In this article, we report a case wherein an eight-year-old girl was treated for one week with three fold the prescribed dose of valproic acid. She suffered from drowsiness, abdominal pain, vomiting, and diarrhea. Her blood tests showed her valproic acid level double the upper limit of normal level in blood and a mild elevation of ammonia. She was treated by discontinuing the medicine, supportive treatment and recurrent doses of activated charcoal. The levels of valproic acid and ammonia returned to normal along with improvement in her clinical condition.While cases of chronic valproic acid intoxication have been reported, no cases of treatment with recurrent doses of activated charcoal for mild chronic valproic acid intoxication has been found in the literature.

**KEYWORDS:** Valproic acid, Intoxication, Activated charcoal, Naloxone, Carnitine

## CASE STUDY

An eight years old girl, who had epilepsy, was treated with a 120 mg dose of sodium valproate as a syrup three times a day .a week before her admission to the Pediatric Department at our institution, she took valproate 600 mg three times a day as a result of a mistaken calculation. Three days before she was admitted she began to suffer from abdominal pain accompanied by vomiting and diarrhea, as well as a tendency to apathy.

The weight of the girl was 20 kilograms, and her Blood Pressure was 109/69, heart rate 92 beats per minute, 100% saturation in room air, the temperature of 36.6 degrees C.

Further physical examination - skin without rash, heart, lungs, and abdomen without abnormal findings, without enlargement of liver or spleen, eyes without pathology, complete normal neurological examination.

### Laboratory

Blood counts-White blood cells are 3800 cells, of which 46% are neutrophils and 42% are lymphocytes, hemoglobin 12.6 g / dl, thrombocytes 265000 / m 3.

Chemistry - Kidney function, blood proteins, glucose level, calcium, phosphorus, sodium, potassium, creatine kinase, liver enzymes, amylase, uric acid, and fats - all within normal range. Gases levels in the blood and lactate levels were also normal. Normal coagulation functions.

The ammonia level at the reception was 49 micromol/liter, where the normal range in the laboratory where the tests were performed was up to 33 micromol/liter.

The blood valproate level was measured at 200 µg / mL. With the therapeutic level being between 50 and 100 micrograms per liter.

Electrocardiogram chart was performed, and it was appropriate for the patient's age.

Computerized tomography examination of the head without any evidence of cerebral edema.

The presence of high levels of valproate in the blood due to overdoses received by the child, many symptoms were noticed including abdominal pain, drowsiness, vomiting, and diarrhea, after consultation with the Israel Poison Information Center at Rambam Medical Center, treatment was initiated as follows - discontinuation of treatment Sodium valproate, fluid infusion, and 10 g of activated charcoal, 5 dosages at a time of 2 hours per dosage.

During her hospitalization, the child continued to complain of abdominal pain and suffered from sleepiness which gradually improved until they completely disappeared. In laboratory follow-up, no significant changes in blood count, renal function, liver enzymes, or clotting function was observed, blood valproate level gradually decreased to 49 micrograms per milliliter one day after her admission to the department.

Two days later, due to her excellent general condition, and the absence of abdominal pain, sleepiness, vomiting or diarrhea, and in light of the standard laboratory tests, including the average level of valproate in the blood she was discharged from the hospital with a recommendation to resume the previous treatment valproate.

## DISCUSSION

Over-dosage poisoning is a medical challenge. Treatment is based on some principles: supportive treatment, antidote, gastric lavage and the provision of absorbent substances such as activated charcoal in order to remove from the bloodstream a substance that has already been absorbed in it, urinary output must be increased, and acidity changed. Also, artificial evacuation options should be considered such as hemodialysis, hemofiltration, hemoperfusion.[14]

The use of gastric lavage as an action to remove toxin has been known for hundreds of years. It is also known that the maximum efficiency in this action is achieved if it is performed close to the time of ingestion of the toxin, as well as in cases where it is known that the patient has swallowed a substance that disturb the emptying of the stomach or material with a delayed release. Gastric lavage is also an advantage in patients who have swallowed large amounts of toxin, a condition that puts their lives at risk immediately.[15] On the other hand, it is important to remember that many complications have been reported, the most dangerous risk is aspiration pneumonia, other complications include laryngospasm, hypoxia, epistaxis, bradycardia, hypochloremia, hyponatremia, water intoxication, or mechanical injury to the stomach. The medical literature describes several cases in which intensive care hospitalization was required due to complications of this procedure.

The use of activated charcoal as a treatment for poisoning is widely used. It is known that activated charcoal can absorb a large number of substances. Therefore it is used to remove substances that have been swallowed from the upper GI tract. The administration of one dose of activated charcoal prevents the absorption of toxic substances from the digestive system to the blood.

It is also known that activated charcoal significantly absorbs the toxin that is already absorbed into the bloodstream. It is important to note that there are substances that activated charcoal does not absorb, such as alcohol, cyanide, and metals such as iron and lithium. It is also not recommended to use active charcoal in cases of caustic or acidic substances poisoning, which can cause local damage to the lining of the digestive tract.

Treatment of repeated doses of activated charcoal every 4 to 6 hours can speed up the process of removing the accumulated substance from the bloodstream back to the intestine, such as Aspirin, Carbamazepine, Dapsone, Phenobarbital, Phenytoin, Theophylline. They are using the Intercapillary Exsorption or Gastrointestinal dialysis process. This action is affected by the blood flow and the active charcoal dosage given.[17] It was also found that the provision of repeated doses of activated charcoal reduces the chance of dismantling the complex between activated charcoal and poison, thereby reducing the risk of re-absorption of the poison into the bloodstream.[16]

There is an excellent consensus in literature shows that repeated doses of activated charcoal lead to more significant absorption of the drug from the bloodstream. However, there is a lack of controlled studies that demonstrate a reduction in mortality or complications due to drug overdose poisoning .

Therefore, there is a recommendation for the provision of repeated doses of activated charcoal only in life-threatening doses of drugs such as phenobarbital, theophylline, dapsone or aspirin.[18]

Besides, with supportive treatment, which is the primary treatment for patients suffering from drug poisoning, the provision of activated charcoal is a useful, simple, effective and inexpensive method to treat poisoning. The success of active charcoal treatment makes it possible to avoid invasive methods such as hemodialysis. For these reasons, the treatment of active charcoal is an integral part of the initial treatment of poisoning.[16]

Valproic acid is a branched short-chain fatty acid and a derivative of valeric acid and its molecular weight 144 Dalton. The mechanism of action of valproate as a drug is the indirect elevation of Gamma-Amino Butyric Acid (GABA) concentration in the brain.[2] Elevation of GABA causes brain suppression. Naloxone treatment with valproate overdose is intended to improve this

suppression because it suppresses the effect of the drug on the elevation of the suppressing neurotransmitter.[9]

Valproic acid is absorbed entirely in the intestine and rapidly affects the central nervous system. This drug has a significant link to proteins estimated as 90-95%. The amount of free valproic acid depends on its overall blood concentration. For example, when the concentration of the drug is 75 mg / L, its free concentration in the blood is about 10% of its general concentration. In a double dose of 150 mg / L, its free concentration will be affected in the same way. This principle is a physiological basis for the use of dialysis in acute poisoning.[3]

The treatment of activated charcoal is also based on this explanation, since the drug found freely in the blood is the drug that can be soaked by activated charcoal, so that in acute toxicity, in which the amount of free drug in the bloodstream is high, it is recommended to be treated by activated charcoal.[11,12] 3-5% of valproic acid are excreted through urine,[4,5] the rest is metabolized in the liver through the conjugation process.

As part of the process, dissolution products are produced, some of which are secreted through bile juices, reach the duodenum and are absorbed back into the bloodstream through the enterohepatic circulation. This process is another physiological explanation for the effectiveness of the use of active charcoal in valproic acid poisoning. In addition to the conjugation process, valproic acid is oxidized by CYP450 proteins in the liver. This process also produces decomposition products, and some are toxic to the liver tissue, hyperammonemia, as demonstrated in our patient, is an expression of this process. In more severe situations, a state of cerebral edema may develop.[6]

Valproic acid poisoning may result in a number of life-threatening conditions, including: cerebral suppression that may lead to respiratory insufficiency and the need for respiration, hypotension, electrolyte disturbance in the blood, disturbance of the acidity in the blood,high ammonia levels,[3,7] encephalopathy, bone marrow suppression, hepatic disorder, acute pancreatitis,[8] and cerebral edema.[2]

Activated charcoal as a treatment in drug poisoning is widely used. In a study that examined the efficacy of active charcoal therapy during the valproic acid poisoning, was demonstrated by a decrease in the absorption of the drug into the bloodstream by approximately 65%.[19]

The provision of activated charcoal by skilled professionals is also recommended in asymptomatic patients who took an overdose of the drug, even before they reached the hospital. The half-life of the drug ranges from 5 to 20 hours and can last up to 30 hours with an overdose of the drug.[5,6,12] There is evidence that treatment with repeated doses of activated charcoal, during acute poisoning with valproic acid, reduces the half-life of the drug to 8 hours or less. An explanation for this is the efficacy of removing excess amount of the drug from the bloodstream by activated charcoal.[11,12]

Some studies have demonstrated efficacy in active charcoal re-treatment in delayed discharged patients who took valproic acid overdose or patients who took very high doses.[20] On the other hand, another study shows that active charcoal did not change pharmacokinetics in patients taking valproic acid. It is known that a toxic level of valproic acid leads to the suppression of mitochondrial oxidation processes, an expression of which is an increase in acylcarnitine levels.[7]

The scientific literature presents some cases in which one of the reasons for the liver failure, expressed in encephalopathy and hyperammonemia, was the accumulation of acylcarnitine and the lack of carnitine. This understanding is a basis for the use of carnitine in patients presenting with these complications.[8] A literature review proves the efficacy of carnitine therapy in valproic acid and poisoning in patients with elevated levels of ammonia, no side effects were noted for this treatment.[10]

The current recommendation for the treatment of carnitine in patients with cognition changes is a primary dose of 100 mg/kg, in addition to repeated doses of 50 mg/kg every 8 hours, until the levels of ammonia in the blood return to the normal range or until clinical improvement of the patient. In vitro hemorrhagic extracorporeal is an effective method of severe oral and acid toxicity, especially when the drug is over 850 mg / L or the patient suffers from the coma, hemodynamic suppression, severe hyperammonemia, or electrolyte or acidic unbalance.[13,3,1]

In this article, we reported a case in which an eight-year-old girl was admitted to our hospital suffering from apathy accompanied by abdominal pain, diarrhea, and vomiting, a clinical picture that began several days before she was admitted. It is known that she has epilepsy and she is treated with valproic acid 120 mg three times a day her weight is 20 kg.

It was found that the dosage taken by the child was four and a half times higher than the dose recommended for her and was equal to 600 mg, three times a day, the dose she took for about a week, during her admission, the child was hemodynamically and respiratory stable.

In the laboratory tests performed in the framework of the investigation, a drug level of 200 was demonstrated, leukopenia and a high blood level of ammonia in the blood was noticed, liver function, liver enzymes, and diastase were normalized, as well as coagulation functions, electrolyte disturbance was also ruled out.

In fundus examination and brain imaging, brain edema was excluded. As she was admitted, the valproic acid treatment was discontinued, and the child was closely monitored for vital signs throughout her hospitalization. Also, she was treated with IV fluids, and after consulting with the Israel Poison Information Center at Rambam Medical Center, it was decided to take active charcoal orally. In a dose of a half gram per kilogram in repeated doses, until the blood glucose in the blood was reduced to 50 micrograms per liter and the patient's clinical improvement was improved. Forty-eight hours of follow-up and care, the child was released into her home in a good general condition and with a recommendation for continued anticonvulsive treatment of acid and prophylaxis, at an acceptable dosage, under close neurological surveillance.

## SUMMARY

Drug poisoning, as a result of overdose therapy, is a common problem in patients who come to the emergency department. As we demonstrated in the discussion in our articles, there are many methods for dealing with these situations. In the case presented in the article, an unusual treatment of repeated doses of activated charcoal was shown in mild to moderate chronic toxicity of valproic acid. This treatment was supported in the scientific literature, especially in studies that described acute toxic effects of valproic acid.

Some of this drug is secreted through bile juices toward the duodenum allows the active charcoal that is given orally to absorb it. Further understanding, due to the increase in the level of free drug in blood during poisoning, when the level of the drug in the blood is high, and there is a saturation of the proteins carrying it in blood, accelerates the removal of the free drug from the bloodstream by the activated charcoal, which explains its effectiveness in these situations.

This method of using gastrointestinal dialysis using activated charcoal has been demonstrated to be effective in our case, which encourages continued use of this method.

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