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Case report

Valproic acid malabsorption in 30 year-old female patient – Case study

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ABSTRACT

Aim: Valproic acid (VPA) is used in epilepsy treatment and as a stabilizer in bipolar affective disorder for over 40 years. Although, the pharmacokinetic properties of valproic acid are well known, it is often forgotten that the formulation of the drug significantly influences its gastrointestinal absorption.

Case: We are describing the case of 30 year-old female patient, diagnosed at the age of 13 with juvenile myoclonic epilepsy. Complete ineffectiveness of the treatment was caused by malabsorption of sodium valproate and valproic acid in the patient. The change of the drug formulation resulted in a several times higher bioavailability of the drug and a partial improvement of the patient's clinical condition.

Commentary: Low concentration of valproic acid after administration the slow-released tablets are usually observed. However, a low bioavailability beside the bad compliance should be considered when the minimal level is extremely low during therapy. It is known that form of the drug, beside presence of food and its components, as well as gastrointestinal tract condition or interactions with other drugs can influence the drug level. Modification of the formulation of the drug may lead to improvement of absorption and increase its effectiveness.

1. Introduction

Valproic acid has been used in medicine since 1970s. At the beginning it was administered for the treatment of partial-onset and generalized seizures, at present it is used to stabilize mood, in paroxysmal hemicrania prophylaxis, and in the treatment of mental illnesses.

Valproic acid can be applied in a wide range of indications due to its multi-directional effects. It influences the level of γ-aminobutyric acid (GABA) in the brain and blocks the voltage-gated ion channels. Experiments conducted *in vitro*, as well as *in vivo*, revealed that valproic acid inhibits GABA transaminase (*ABA7*) and succinic semialdehyde dehydrogenase (*ALDH55A1*), enzymes involved in GABA metabolism. The above- mentioned mechanism results in an increase of

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GABA concentration and GABAergic activity, which is impaired in epileptic seizures. [1] The anticonvulsant effect is also due to a decrease of neuronal discharges by blockade of the voltage-gated sodium, potassium and calcium channels, as well as inhibition of depolarization initiated by the NMDA receptor, and modification of cellular signaling pathways, such as kynurenine pathway [1–5]. Its multi-directional mechanisms of action are believed to be responsible for a very high effectiveness in different types of seizures.

In clinical practice, valproic acid (sodium salt) is administered parenterally, orally and rectally. The most common oral formulations include syrup, suspension, immediate-release or prolonged-release tablets and enteric-coated tablets. The rate of absorption of oral preparations depends on the form of the drug, and it is the highest, when administered in solution [6]. Bioavailability of the drug is believed to be comparable for different oral formulations.

The drug highly bounds to blood proteins, mainly albumins (87–95%) with low plasma clearance (6–20 ml/h/kg). Bounding decreases with increasing drug concentration in the blood. The therapeutic plasma concentration of valproic acid in long-term therapy varies between 40 and 100 μg/ml (280–700 μmol/L). Less than 3% of the drug is excreted in an unchanged form with urine. The remaining part undergoes biotransformation in the liver. Valproic acid belongs to fatty acids and, consequently, is metabolized *via* endogenous pathway in mitochondria: through mitochondrial β-oxidation, microsomal ω and (ω-1)-hydroxylation, glucuronidation and other conjugation reactions. It is excreted mainly with urine, trace amounts can be also present in the bile, feces and breath. The main metabolite excreted with urine is valproate glucuronide [7–9].

In everyday clinical practice, absorption is rarely regarded a significant pharmacological parameter. In this paper, we would like to highlight essential differences between the concentration and bioavailability of valproic acid in different formulations.

2. Case study

A 30 year-old female patient with juvenile myoclonic epilepsy, diagnosed at the age of 13, was followed up in the hospital outpatient clinic from the age of 22. The patients suffered from generalized tonic–clonic, myoclonic and absence seizures with different frequency since the onset of the disease. Myoclonus occurred most frequently (a few times every day), typically in the morning, in upper extremities, but sometimes was extremely severe, making the patient fall. Generalized tonic–clonic seizures were less frequent, about 1 per month, absence seizures about 2 per week. The patient graduated from secondary school and did not continue education because of frequent seizures. Cognitive functions did not deteriorate in the course of the disease. Since her adolescence the patient was affected by obesity, arterial hypertension and bronchial asthma. From the beginning of the disease the patient was treated with high doses of valproic acid (prolonged-release drugs), not achieving its full effect. Additionally, the patient received lamotrigine and levetiracetam for about 5 years. All drugs were used at maximum acceptable doses. There were no seizure free periods in the course of the disease. In 2014 the patient was admitted to our hospital for observation due to increased number of seizures. EEG revealed numerous generalized paroxysmal discharges in the form of spike-polyspike-slow wave synchronized complexes (Fig. 1). The valproic acid level during hospitalization in fasting state was 6 μg/ml. A daily dose of valproic acid with sodium valproate in the form of prolonged-release drug was 2000 mg. As the patient denied non-adherence to therapy, numerous evaluations of valproic acid level were carried out, after administration of the recommended dose of the drug. Valproic acid level was determined before drug intake, as well as 2 and 6 h after oral administration of sodium valproate with valproic acid in the form of prolonged-release tablets (1000 mg). The results indicated malabsorption of the drug (valproic acid level before administration – 4.92 μg/ml; 2 h after the morning dose – 8.10 μg/ml; 6 h after the morning dose – 18.49 μg/ml). Since the patient was discharged due to family reasons, the formulation of the drug was changed to enteric-coated fast-releasing tablets. Two weeks later the patient was admitted to hospital again. The drug level in fasting state was at 33.92 μg/ml (2000 mg/day). The concentration of valproic acid was determined in the fasting state, as well as 2 h and 6 h after intake of 1000 mg sodium valproate in form of syrup, enteric-coated tablets, and after intravenous injection. The concentration of valproic acid 2 and 6 h after administration was 62 μg/ml and 47 μg/ml, respectively, for syrup, 103.81 μg/ml and 94.72 μg/ml for enteric-coated tablets, and 45.5 μg/ml and at 52 μg/ml for intravenous administration. The trial revealed normal absorption of syrup and enteric-coated tablets, therefore enteric-coated tablets therapy was maintained. The daily dose was increased to 3000 mg/day. Decreased number of seizures was achieved during next 4 weeks, as well as improvement of EEG recording (no abnormalities). At present, generalized tonic–clonic seizures occur about once a year, the frequency of myoclonus and absence seizures has also decreased. Valproates level in fasting state after a few weeks was 58.78 μg/ml.

3. Discussion

Gastrointestinal absorption and bioavailability of drugs, including valproic acid, depend on the type of preparation. In our patient malabsorption of sodium valproate with valproic acid in prolonged-release tablets occurred, with normal drug concentration after its administration in the form of syrup and enteric-coated tablets.

Gastrointestinal absorption is influenced by drug formulation. There are many publications comparing absorption depending on the formulation. Chun et al. indicated that absorption rate of valproic acid in syrup is higher than in capsules. The absorption rate was higher in fasting state and directly before a meal than after a meal. Bano et al. compared the pharmacokinetics of valproic acid in healthy volunteers after administration in capsules, tablets and syrup. Following the administration, maximum concentration and the time to peak maximum concentration were the highest for syrup, and the lowest for capsules. Bioavailability of the drug in capsules was also lowest. In our patient the drug concentrations were significantly higher when administered in enteric-coated

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