REVIEW

VALPROATE INDUCED SUBCLINICAL HYPOTHYROIDISM IN CHILDREN WITH EPILEPSY

Raluca Teleanu[1,2], Margarita Matei[3], Magdalena Sandu[2], Smaranda Nita[1]

[1]Department of Pediatric Neurology, "Dr. Victor Gomoiu" Children's Hospital, Bucharest
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest
[3]Endocrinology Ambulatory, "Dr. Victor Gomoiu" Children's Hospital, Bucharest

ABSTRACT

Stroke remains a leading cause of disability and mortality all over the world despite the efforts made towards improving treatment. Most of the clinical studies have not shown significant beneficial effects in the evaluation of various molecules for their neuroprotection and neurorecovery promoting properties. The new concept of multimodal, pleiotropic drugs has opened new perspectives in this field. This review focuses on clinical stroke studies with biologically active molecules such as erythropoietin, granulocyte-colony stimulating factor and Cerebrolysin.

Key words: neuroprotection, neurorecovery, multimodal, pleiotropic drugs

Valproic acid (VPA) is one of the most effective broad-spectrum and extensively used antiepileptic drugs available for treatment of both generalized and partial epilepsies in children. The most recognized adverse reactions encountered in VPA therapy are hepatotoxicity, thrombocytopenia and other hematological abnormalities as well as weight gain, the latter especially affecting females. Additionally, dysmenorrhoea and amenorrhoea in women treated with VPA are well documented side effects. Despite previously negative correlations between VPA therapy and subclinical hypothyroidism in children, an increasingly number of studies show contrasting results, leaving room for possible implementation of screening programs for evaluation of thyroid function in children undergoing anticonvulsant therapy with VPA.

VPA (dipropylacetic acid) is a fatty carboxylic acid. Its anti-seizure activity is presumed to be greatest for carbon chain lengths of five to eight atoms. Although having been used as an antiepileptic drug since the 1960s, its main mechanism of action remains unknown and its effects are believed to result from a combination of multiple mechanisms, accounting for its broad spectrum of action. VPA is thought to block high – frequency repetitive firing of neurons by inhibiting voltage – sensitive sodium channels and, at high concentrations, to activate calcium dependent potassium conductance. VPA also has a GABAergic effect, through elevation of GABA levels in the brain, believed to result from various mechanisms such as an inhibitory effect on GABA transporter GAT – 1 as well as on GABA – transaminase and facilitating glutamic acid decarboxylase. However, VPA effects on GABA metabolism are observed only at high valproate levels. Blockade of NMDA receptor-mediated excitation is also one of the discussed mechanisms of action.

Adverse reactions encountered with the use of VPA in children encompass a wide range of effects on numerous systems and organs such as cardiovascular, gastrointestinal, genitourinary, central nervous system, dermatologic, neuromuscular, ocular, respiratory, hematologic. Hepatic toxicity resulting in fatal hepatic failure, especially in children less than two years of age who undergo polytherapy, with congenital metabolic disorders and/or organic brain disease, is the most feared ad-

Author for correspondence:
Assoc. Prof. Raluca Ioana Teleanu MD, PhD, "Dr. V Gomoiu" Children's Hospital, Department of Pediatric Neurology, 21 Basarabia Bd, Zip Code 022102, Bucharest, Romania
e-mail: ralucate@gmail.com

verse reaction encountered. Transient elevation of liver enzymes has also been observed. The most common hematological adverse reactions are thrombocytopenia and prolonged bleeding time. The effects of VPA on the endocrine and metabolic system cited so far include amenorrhea, dysmenorrhea, weight gain as well as hyperammonemia, carnitine deficiency and impaired fatty-acid oxidation. However, growing attention is being paid to the effects of VPA therapy on the thyroid function.

The pathways of thyroid hormone synthesis, secretion, transport throughout the body and metabolism offer many sites of drug interaction. Currently, testing for thyroid function is common in clinical practice, as a wide range of medication is already known to affect it. The thyroid profile studied included measurements of triiodothyronine (T3), thyroxine (T4), free T4 (FT4), basal thyroid-stimulating hormone (TSH) as well as stimulated TSH (post – administration of thyrotropin releasing hormone – TRH). TSH, secreted by the thyrotrope cells of the anterior pituitary is of maximal importance in the regulation of the thyroid axis and constitutes the best indicator of thyroid function in clinical practice, because of its high sensitivity to changes in serum thyroid hormone levels. Subclinical hypothyroidism refers to elevated levels of plasma TSH while plasma levels of thyroid hormones, T3 and T4, stand within normal limits.

Antiepileptic drugs such as Carbamazepine, Phenobarbital and Phenytoin have been cited to alter the levels of thyroid hormones, by interfering with their hepatic metabolic pathways, namely causing induction of microsomal enzyme systems.

VPA is metabolized in the liver via glucuronide conjugation and oxidation, as are, to a small extent, T3 and T4. However, there are contrasting results in clinical trials carried, in different conditions, throughout the years, on the possible role of VPA in affecting the thyroid function, in children. While various studies point to no effect of VPA on the thyroid function, a number of clinical trials found significant alterations of plasma TSH levels following long-term administration, accounting for subclinical hypothyroidism. Moreover, some studies cite the same effect after relatively short periods of time following initiation of VPA therapy. It should be noted that, on most occasions, discontinuation of VPA therapy lead to normalization of the thyroid parameters.

Despite being a widely used and already extensively studied antiepileptic drug, the increasingly positive correlations between VPA therapy in children with epilepsy and induction of subclinical hypothyroidism, as well as the relatively scarce information on the mechanisms involved, suggest that more attention should be paid to implementation of standard thyroid tests to aid in prospective studies.

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