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Editorial

Topiramate and Nutritional Disorders

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Editorial

Many anti-epileptic drugs that can interfere with nutrition with consequent changes in body weight; some of these drugscan determine an increase, others a decrease of Body Mass Index (BMI). Among the drugs that induce weight loss, Topiramate (TPM), a new generation anti-epileptic drug, presents a very important anorectic potentiality.

TPM, which interacts with multiple neurotransmitter and enzyme systems, has been approved by the Food and Drug Administration to treat seizure disorder, prevent migraine, and (in combination with phentermine) to reduce weight [1]. In particular, in the contextof epileptic syndromes, TPM is used for the treatment of partial seizures, Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, refractory and frontal lobe epilepsy and other types of epilepsy (e.g. childhood absence epilepsy) [2].

TPM is a fructose-derivative tetrahydropyrane with one sulphonamide attached. Two acetal groups with two methyl groups each are attached to the molecule to protect the substituents [3].TPM present multiple mechanisms of actions, that lead to the reduction of neuronal excitation: in fact, it blocks voltage-gated sodium channels, inhibits kainate-type glutamate receptors, decreases L-type voltage-sensitive calcium currents, increases the opening of GABA-mediated chloride channels, inhibits carbonic anhydrase and increases the potassium conductance.

Aboutthe effectof TPMon weight loss, althoughthe pathogenetic mechanismsare notyet fullyknown, there are at the present many studies on animals and humans that analyzed these aspects.

In the animal studies, TPM induces weight loss throughdifferent mechanisms of action: it reduces energetic efficiency stimulating lipoprotein lipase activity in brown adipose tissue and skeletal muscle, resulting in an increase of thermogenesis and substrate oxidation. Moreover, some studies [4,5] suggest the hypothalamic involvement in weight-loss. TPM increases Neuropeptide Y (NPY), galanin and corticotrophin-releasing hormone that play an important anorexigenic role within the hypothalamus. Various animal studies [6-8]show that TPM increases insulin sensitivity, decreasing insulinemia through a concomitant reduction of food intake, an enhancement of insulin-mediated suppression of hepatic glucose output and an improvement of the insulin action in the adipose tissue.

On the other hand, human studies [9,10] demonstrate the role of reduced caloric intake, hormonal involvement, changes in glucose and lipid metabolism. TPM increases the adiponectin levels with a consequent increased lipid oxidation, insulin sensitivity and decreased lipocytes in the pericirculatory system as well as triacylglycerol in liver and musculature. Moreover, leptin is another important factor that could be influenced by TPM treatment; leptin is a protein hormone biosynthesized and secreted by adipose tissues that regulates body energy metabolism, binds with the leptin receptor in the hypothalamus, and modulates the secretion of neuroendocrine hormones such as NPY.The role of TPM on the leptin activity is controversial: some studies [11,12] found that TPM treatment reduces leptin levels, while other authors [13] suggest that the change of leptin is not a key mechanism for the weight loss after TPM treatment. Also, weight loss could be associated with improvements in glucose, insulin, cholesterol levels.

Finally, some factorsseem to be relatedwithnutritional disorders and weight loss: in particular, the duration of the treatment and a high baseline BMI of the patients are important risk factors for this adverse effect. Weight loss was observed most frequently during the first four-six months of treatment, and continued for at least one year and was associated with sustained fat loss. Moreover, a predictor factor of weight-loss during the therapy with TPM is the overweight at the beginning of the treatment; in particular the loss of weight is greatest in patients with highest BMI; this side effect is important and should be considered before initiating treatment.

TPM may be considered as treatment of choice in obese patients with various types of epilepsy, although in children and in the patients with neurodevelopmental disorders it is necessary to be careful about their nutritional vulnerability.

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