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Effectiveness of topiramate in lipomatosis comorbid with agoraphobia and migraine

Case study

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Summary

Topiramate has been used in epilepsy and migraine for more than ten years. Recently, it has gained importance in the treatment of obesity, particularly in combination with phentermine. We report the case of a 51-year-old woman suffering from agoraphobia with panic attacks, diabetes and migraine. In addition, she simultaneously developed generalized lipomatosis leading to a weight gain of more than 20[th]kg. She was given topiramate up to 100[th]mg per day in addition to an SSRI (citalopram) and a melatoninergic drug (agomelatine). Gradually, within two years after starting topiramate, she lost 20[th]kg, with a corresponding reduction of thorax and arm circumference. Although the mechanism of weight loss remains to be clarified, topiramate may be an alternative approach in patients suffering from generalized lipomatosis.

agoraphobia with panic attacks / diabetes / lipomatosis / migraine / topiramate / weight loss

In 1996 the anticonvulsant drug topiramate was approved by the US Food and Drug Administration (FDA) and has also gained importance in the prevention of migraine [1-3]. Moreover, topiramate was investigated as a treatment in personality disorders, alcoholism and substance addiction, for instance to cocaine or methamphetamines [4, 5]. A common side-effect of topiramate, its anorectic effect, gradually became a clinical treatment option for obesity [6], which has led to the successful use of a topiramate-phentermine formulation in adult obesity [7-9]. In psychiatry topiramate was also assessed in post-traumatic stress and bipolar disorders or social phobia, without unambiguous effects [10-12].

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Topiramate has a bioavailability of approximately 80% and reaches the maximum concentration within 2 to 4 hours after oral administration. Oral dosage starts low, with 25 mg s.i.d. or b.i.d. and is gradually increased to daily doses of up to 100 mg in migraine and 400 mg in epilepsy. About 80% of the dose is excreted unchanged in urine with a half-life of approximately 20 hours. The pharmacology of this unusual anticonvulsant, whose chemical structure is a sulfamate-substituted monosaccharide, has not yet been completely expounded [1]. Analogously to acetazolamide, topiramate inhibits the carboanhydrase isoenzymes, blocks voltage sensitive sodium channels (VSSC), increases the activity of gamma-aminobutyric acid (GABA)-A receptors and decreases the activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor or kainite (i.e. glutamate) receptors [13, 14]. Apart from the inhibition of carboanhydrase, topiramate inhibits the CYP2C19

and induces the CYP3A4 enzymes, which is particularly important with regard to oral contraceptives after administration of doses above 200 mg per day [15]. The drug is generally well tolerated and safe in clinical doses [16].

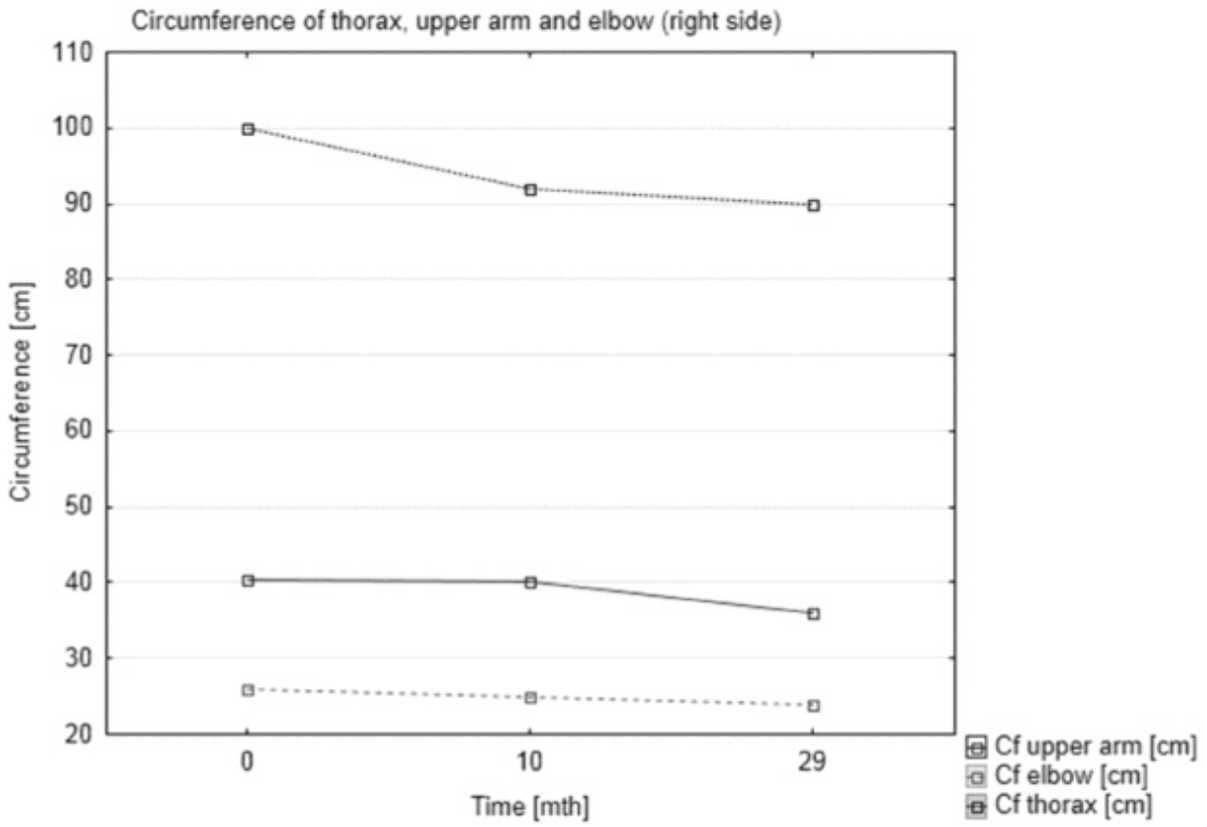
Classical indications for topiramate use are partial-onset or primary generalized tonic-clonic seizures, both as monotherapy and as adjunctive treatment, in children from 2 years of age or older and adults, especially in patients with Lennox-Gastaut syndrome [2, 14]. Recently, topiramate was approved in the USA in combination with phentermine, an amphetamine derivative, as a new approach to helping weight loss.

Lipomatosis symmetrica (Launois-Bensaude syndrome) is characterized by diffuse hyperplasia of adipose tissue. With regard to the distribution pattern of fat tissue, several types of lipomatosis can be distinguished: Madelung's disease of the neck, shoulder, limb-girdle or abdominal type [17-20]. The aetiology of the disease has not yet been elucidated, but familial (autosomal-dominant transmission) or metabolic (diabetes, hypothyroidism) factors, certain medications (e.g. HIV drugs, peroxisome proliferator-activator receptor gamma (PPAR-γ) agonists, steroids, chemotherapy) and diet (alcohol) are associated with the disorder. Interestingly, in lipomatosis fat cells show autonomous proliferation, being resistant to catecholamine lipolytic effects [21]. To date, no evidence-based treatment has been established. Some interventions such as liposuction or operations show a high relapse rate. Diet alone also seems to be ineffective, whereas ß-receptor agonists such as salbutamol showed some promising results in case reports [22].

CASE REPORT

A 51-year-old woman with anxiety was referred to an out-patient clinic due to severe agoraphobia with panic attacks (ICD-10 F40.01). She reported psychosocial problems (various severe diseases and suicide in her social and family environment, divorce, unemployment), which had

Figure 1: Circumference of right mid-upper arm, elbow and thorax (below breast) during treatment with topiramate.



caused a depressive mood with loss of energy, and a diagnosis of an adjustment disorder (ICD-10 F43.2) was also postulated. Migraine and a transient abuse of alcohol a few years previously with steatosis hepatis were documented. She had smoked 10 cigarettes per day for years. Her body weight was 66 kg and she was 1.62 m tall.

On admission she complained of extreme phobic fear concerning heights, buses, stores with crowds of people that she had experienced for many years. In these situations she experienced fear with heart palpations, tachycardia, perspiration, unrest, tingling in the legs, dizziness, loss of control and sometimes diarrhea or pollakisuria. Leaving the scene or avoiding it altogether relieved the symptoms. She became more and more desperate and had suicidal ideations. Clinical examination, clinical laboratory and an electrocardiogram (ECG) did not reveal clinically relevant findings. She was integrated in an out-patient psychotherapy setting and got a selective-serotonin reuptake inhibitor (SSRI; citalopram 20 mg) as well as 7.5 to 15 mg mirtazapine to facilitate sleep. Within a few months she recovered almost completely and was able again to manage her everyday life.

Apart from the psychiatric disorder, she had developed lipomatosis (ICD-10 E88.2) prior to the first out-patient consultation and was treated by an endocrinologist. She had noticed weight gain over a few months with a swelling of the upper arm, shoulder and thigh, with a very unpleasant cosmetic appearance. Local pain was tolerable without specific medication. As agoraphobic complaints decreased, she was more and more concerned about the lipomatosis on the one hand and migraine on the other hand. She complained of a weight gain from 60 kg up to 87 kg within 6 months, which was accompanied by diabetes requiring treatment. She was administered metformin and her mirtazapine was – for reasons of precaution – replaced by agomelatine. Due to almost monthly migraine attacks she asked for a preventive medication and was additionally prescribed topiramate up to 100 mg per day. The medication was well tolerated and migraine attacks came to an end within a few months. Within one year she gradually lost her excess weight, from 87 kg to 67 kg.

Apart from the preventive effect on migraine attacks, she felt very happy owing to weight loss and her physiotherapist could verify a reduction of her arm and thorax circumferences (Fig. 1). As a consequence of the resolution of lipomatosis, her agoraphobia and panic attacks also subsided so that she only needs a consultation in the out-patient clinic twice a year.

DISCUSSION

We report the case of a 51-year-old woman suffering from lipomatosis who obviously responded to treatment with topiramate. Influence of mirtazapine was considered, however, the dose had been low and retrospectively, the patient insisted that symptoms occurred prior to mirtazapine prescription. Topiramate facilitates weight loss in patients and may be a good option in individuals with obesity suffering from seizures or migraine [23]. The exact metabolic mechanism has not been elucidated yet, although effects of topiramate on the hypothalamus are discussed by Yaman et al [24]. Other studies suggest a significant role of increased adiponectin in conjunction with lower leptin levels responsible for weight loss after topiramate intake [25, 26]. Adiponectin – secreted almost exclusively by the adipose tissue itself – is postulated to play a decisive role in weight reduction [27]. A third hypothesis suggests that carboanhydrase, particularly isoenzyme II (CA II), may be involved in lipogenesis and therefore CA-inhibitors such as topiramate or zonisamide show anorectic properties [28]. The role of vascular endothelial growth factor, which transiently increases after intake of topiramate, needs clarification [26].

The patient did – irrespective of the underlying pharmacological mechanism – benefit substantially from topiramate treatment, losing about 20 kg of body weight. She felt well and even-tempered following administration of topiramate so that a positive effect on the mood may be an additional welcome "side-effect". Her migraine ceased and the patient does by no means refuse to change topiramate medication. Migraine is an approved indication for topiramate, but it should be kept in mind that its use in obesity is off-label in Europe. However, it may be an option in severely overweight individuals and especially in those suffering from lipomatosis.

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