

Paradoxical weight gain after introduction of topiramate associated to fluoxetine withdrawal

Ganho de peso paradoxal após a introdução de topiramato associado à retirada de fluoxetina

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RESUMO

Os casos de duas mulheres tratadas para migrânea transformada que apresentaram ganho de peso após a introdução de topiramato são relatados. O topiramato tem sido relatado como efetivo para o tratamento de diversas condições, incluindo epilepsia, transtornos do humor, migrânea e migrânea transformada. Perda de peso é um de seus efeitos colaterais mais comuns, havendo sido relatada por até 90% dos indivíduos usando a medicação. As duas pacientes relatadas apresentaram perda de peso paradoxal após a introdução de topiramato para o tratamento de migrânea transformada. Ambas haviam descontinuado recentemente a fluoxetina, e uma havia descontinuado femproporex. Cuidado deve ser tomado por ocasião da introdução de topiramato em pacientes nos quais fluoxetina ou anfetamínicos estejam sendo descontinuados uma vez que estas situações podem ser predisponentes ao ganho de peso.

PALAVRAS-CHAVE

Topiramato, migrânea, ganho de peso, fluoxetina, anfetamina.

ABSTRACT

The case of two women who presented a paradoxical weight gain after the introduction of topiramate is reported. Topiramate has proved to be effective for the treatment of several conditions, including epilepsy, mood disorders, migraine and transformed migraine. Weight loss is one of its most frequent side effects, occurring in up to 90% of the individuals that take the drug. The two female patients herein reported presented marked paradoxical weight gain after the introduction of topiramate for the therapy of transformed migraine. Both had recently discontinued fluoxetine, and one had also recently discontinued femproporex. Care should be taken while introducing topiramate for patients in whom fluoxetine or amphetamines had been recently discontinued, since these may be predisposing conditions for a topiramate-associated paradoxical weight gaining effect.

KEY WORDS

Topiramate, migraine, weight gain, fluoxetine, amphetamine withdrawal.

Topiramate, a new anti-epileptic drug, which has increasingly been used in the preventative therapy of transformed and episodic migraine,¹⁻³ has a well-known weight-losing effect that can be perceived already in the first month of therapy in up to 90% of the patients using it.⁴ Although the manufacturer mentions the possibility of weight increase as a consequence of topiramate use (Prod Info Topamax®, 1999) we were not able to find any detailed report of topiramate-associated weight gain. The cases of two patients in whom weight gain was observed after topiramate was prescribed for transformed migraine prophylaxis are reported, and the possible role of the associated fluoxetine discontinuation is discussed.

CASES REPORTS

Case 1 – A 38 year-old white female had a history of migraine since the age of 8, which had become chronic about 5 years before her first appointment. She used to abuse ergotamine tartrate, taking about 2 mg a day. She had unsuccessfully used amitriptyline before, as well as propranolol for migraine prophylaxis. She suffered from hiatal hernia and had some lower limb varicose veins. After a term pregnancy and a cesarean section, she had an intra-uterine device placed. One of her sisters was schizophrenic, and the other was severely depressed. Her previous CAT-scan and MRI imaging of the head had yielded normal results. She had been taking fluoxetine 20 mg/day for a year. A six-day prednisone 60 mg/day pulse was started, and topiramate 25 mg/day was prescribed and titrated up to 25 mg b.i.d. After two weeks of therapy she reported mild tension-type headaches, but no migraine headaches, although she felt a little sleepy and “numb”. A month later she felt less anxious and less of a binge-eater, but a mild menstrual headache remained. She was still “numb” and mildly insomniac and her memory was compromised. Fluoxetine was reduced to 10 mg/day and slowly discontinued over a month. Two months later, she reported a marked increase in appetite and weight gain after fluoxetine was discontinued. She had gained 6 kg (9.2 pounds) while on topiramate. Her migraine headache had recurred. Thyroid function tests were normal. Fluoxetine was reintroduced without control of the symptoms. Topiramate was discontinued and flunarizine 10mg/day was added to fluoxetine. Currently the patient is almost headache-free with sodium valproate 200 mg/day associated with methysergide 1 mg b.i.d..

Case 2 – A 55 year-old female sought our help with a 15-year history of daily headaches and of daily use of isometheptene mucate and dipirone. She had a previous history of Hashimoto’s thyroiditis, gastroesophageal reflux symptoms, three pregnancies (2 at term) and the use of a birth control pill. She used to take a dose of T4 75 mcg/day for her hypothyroidism, fluoxetine 15 mg/day for

depression and femproporex 15mg/day. She was mildly obese and had varicose veins in her lower limbs. There was temporomandibular joint dysfunction. She was placed on topiramate 25 mg nocte, and returned 2 months later having gained 13 kg (20 pounds), in spite of a complete remission of her headaches and of an improvement in her mood. She said that prior to starting on topiramate she had discontinued the fluoxetine and the femproporex, which had made her lose about 6 kg in the preceding 6 months. Her thyroid function tests yielded normal results. Condition stabilized, despite of the increase in the dose of topiramate to 50 mg/nocte, to control insomnia.

DISCUSSION

Topiramate (TPM) is a novel neurotherapeutic drug currently indicated for the treatment of epilepsy and is undergoing development for other central system indications, including neuropathic pain, bipolar disorder and migraine prophylaxis.

Topiramate can bring about body weight loss in humans.^{4,5} The reason for this effect is not known, but recent studies in animals gave some hints regarding possible mechanisms.^{6,7} In obese rats, topiramate induced a marked reduction in food intake, whereas high doses would be responsible for a reduction greater than 50% of energetic efficiency. The energetic efficiency (energy gain/energy intake), represents an estimate of the amount of energy in food that is stored in tissues. Topiramate inhibits fat deposition while reducing the lipoprotein lipase (LPL) activity in various white adipose tissue depots, but the mechanisms whereby topiramate affects the regulation of the energy balance have yet to be understood.⁸

TPM was also reported to reduce energetic efficiency while it stimulates LPL activity in brown adipose tissue, and to reduce plasma glucose and plasma leptin levels in female rats as well as plasma insulin and liver triglycerides in male animals. In the hypothalamus, topiramate increased mRNA for neuropeptide Y, reduced mRNA for neuropeptide-Y Y1 and Y5 receptors, corticotropin-releasing hormone, and type II glucocorticoid receptors, but had no effect on mRNA levels for the short or long form of the leptin receptor.⁹ The effect of topiramate on energy balance was accounted for by a decrease in energetic efficiency, resulting from an effect exerted by the drug on both energy intake and thermogenesis. There is no influence of the sexual hormones in these process.⁷

Fluoxetine is a selective serotonin reuptake inhibitor used mainly in the treatment of depression. Its use not only has been proved to lead to weight loss,¹⁰ but also has been singled out as helpful in the therapy of binge-eating disorders.¹¹ Furthermore, fluoxetine and topiramate seem to share a supra-additive weight-losing effect.¹² However, the long-term use of fluoxetine might occasionally be

associated to weight increase greater than 7% of the baseline,¹³ which according to other authors may go as high as 30 pounds.¹⁴

Discontinuation of fluoxetine is not reported to lead to marked withdrawal symptoms, probably because of the its long half-life and because of the presence of active metabolites.^{15,16,17} Furthermore, marked weight gain as a fluoxetine withdrawal symptom has never been reported, in spite of its vast worldwide prescription.

Although topiramate has proved to be an effective therapy for monopolar depressive disorder,¹⁸ it has also been reported to aggravate depression symptoms.¹² In this sense, the weight gain reported by the patients described herein could have been an expression of a then undiagnosed, masqueraded depression.

Conversely, fenproporex chloridrate, an amphetamine used like diethylpropyone as a weight-losing pill, may lead to increased appetite as a withdrawal symptom. Amineptine, a dopamine re-uptake inhibitor has been shown to be effective in the control of amphetamine withdrawal symptoms.¹⁹

In the first case, the weight gain that seemed to be more closely related to topiramate introduction remains a puzzle, since it cannot be explained by currently known effects of the drug on the metabolism. In the second case, however, it is more reasonable to attribute the weight gaining effect to fenproporex withdrawal. The effectiveness of topiramate in the therapy of binge-eating disorder would pose it as effective in the therapy of increased appetite related to amphetamine withdrawal. However, the dose used by the aforementioned patient was much lower than that which is used to treat binge-eating disorder, and this might be the reason why topiramate failed to control the symptoms of increased appetite. Weight gain among patients using topiramate seems to be an unusual finding that probably has to be individualized.

REFERENCES

- Krusz JC, Scott V. Topiramate in the treatment of chronic migraine and other headaches [abstract]. *Headache* 1999;39:363
- Von Seggern RL, Mannix L, Adelman JU. Efficacy of topiramate in migraine prophylaxis: a retrospective chart analysis [abstract]. *Neurology* 2000;54(suppl 3):A267-A268.
- Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache* 2001;41:968-975.
- Biton V, Montouris GD, Ritter F. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YRC Study Group *Neurology* 1999;52:1.330-1.337.
- Gordon A, Price LH. Mood stabilization and weight loss with topiramate. *Am J Psychiatry* 1999;156:968-9.
- Picard F, Deshaies Y, Lalonde J, Samson P, Richard D. Topiramate reduces energy and fat gains in leans (Fa/?) and obese (fa/fa) Zucker rats. *Obesity Research* 2000;8:656-63.
- Richard D, Picard F, Lemieux C, Lalonde J, Samson P, Deshaies Y. The effects of topiramate and sex hormones on energy balance of male and female rats. *Int J Obes Relat Disord* 2002;26:344-53.
- Richard D, Ferland J, Lalonde J, Samson P, Deshaies Y. Influence of topiramate in the regulation of energy balance. *Nutrition* 2000;16:961-6.
- York DA, Singer L, Thomas S, Bray GA. Effect of topiramate on body weight and body composition of Osborne-Mendel rats fed a high-fat diet: alterations in hormones, neuropeptide, and uncoupling-protein mRNAs. *Nutrition* 2000;16:967-75.
- Goldstein DJ, Rampey AH Jr, Enas GG, Potvin JH, Fludzinski LA, Levine LR. Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord* 1994;18:129-35.
- Hudson JI, Carter WP, Pope HG Jr. Antidepressant treatment of binge-eating disorder: research findings and clinical guidelines. *J Clin Psychiatry* 1996;57(Suppl 8):73-9.
- Dursun SM, Devarajan S. Accelerated weight loss after treating refractory depression with fluoxetine plus topiramate: possible mechanisms of action? *Can J Psychiatry* 2001;46:287-8.
- Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry* 2000;61:863-67.
- Folgelson DL. Weight gain during fluoxetine treatment. *J Clin Psychopharmacol* 1991;11:220-1.
- Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome. *Biol Psychiatry* 1998;44:77-87.
- Zajacka J, Fawcett J, Amsterdam J, Quitkin F, Reimherr F. Safety of abrupt discontinuation of fluoxetine: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 1998;18:193-7.
- Price JS, Waller PC, Wood SM, Mackay AV. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996;42:757-63.
- Prado-Lima PAS, Bacaltchuk J. Topiramate in treatment-refractory depression. XI World Congress of Psychiatry, Hamburg, Germany, 6-11 August, 1999. Poster 15-3, 126, abstract.
- Jittiwutikan J, Srisurapanont M, Jarusuraisin N. Amineptine in the treatment of amphetamine withdrawal: a placebo-controlled, randomised, double-blind study. *J Med Assoc Thai* 1997;80:587-92.

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