

Methysergide to prevent migraine and cluster headache and the possibility of retroperitoneal fibrosis. Case reports

Metisergida como profilaxia de migrânea e cefaleia em salvas, e a possível ocorrência de fibrose retroperitoneal. Relato de casos

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SUMMARY

BACKGROUND AND OBJECTIVES: Methysergide is a drug with proven efficacy to prevent both migraine and cluster headache, although it may predispose to fibrosis (< 1%). This study aimed at reporting two cases of primary and difficult to control headache, satisfactorily treated with methysergide, which had to be withdrawn due to suspicion of retroperitoneal fibrosis (RF).

CASE REPORTS: Methysergide was successfully used to prevent migraine and cluster headache in a 69-year old male and in a 58-year old female, respectively, both

refractory to first and second line drugs. After 24 months for the first case, and 30 months for the second case, of continuous methysergide, signs and symptoms suggesting RF were observed, such as asymmetric painless lower limbs edema in the migraine patient, and abdominal pain, sexual dysfunction and lower limbs edema in the cluster headache patient. In spite of the early negative screening for retroperitoneal edema made with normal abdominal ultrasound and CT, in the second, since signs and symptoms were progressing, we decided for methysergide withdrawal and decrease, respectively. There has been total resolution of symptoms approximately one week after such approach.

CONCLUSION: Methysergide is a good option for refractory cases, but should be used with caution. Withdrawing the drug every six months for approximately 4 to 8 weeks decreases the incidence of RF, in addition to clinical observation of signs and symptoms suggesting this side-effect.

Keywords: Cluster headache, Headache, Retroperitoneal fibrosis.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Metisergida é fármaco de eficácia comprovada na profilaxia tanto da migrânea quanto da cefaleia em salvas, embora possa predispor a fibrose (< 1%). O objetivo deste estudo foi relatar dois casos de cefaleia primária de difícil controle, satisfatoriamente conduzidos com metisergida, que precisou ser interrompida por suspeita de fibrose retroperitoneal (FR).

RELATO DOS CASOS: A metisergida foi utilizada, com sucesso, como profilático de migrânea e cefaleia em salvas em paciente de 69 anos, sexo feminino, e

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de 58 anos, sexo masculino, respectivamente, ambos refratários aos fármacos de primeira e segunda linha. Após 24 meses, no primeiro caso e 30 meses, no segundo, de uso contínuo de metisergida, foram observados sinais e sintomas sugestivos de FR como edema assimétrico de membros inferiores, sem dor, na paciente com migrânea; dor abdominal, disfunção sexual e edema de membros inferiores, no paciente com cefaleia em salvas. Apesar do rastreio inicial negativo para fibrose retroperitoneal feito com ultrassonografia e tomografia computadorizada de abdômen normais, no segundo, como os sinais e sintomas estavam progressivos, optou-se pela suspensão e redução, respectivamente, da metisergida. Houve resolução completa do quadro cerca de uma semana após essa conduta.

CONCLUSÃO: A metisergida é boa opção nos casos refratários, mas deve ser utilizada com cautela. Estratégia de descontinuidade do fármaco a cada seis meses, por cerca de 4 a 8 semanas, reduz o risco de ocorrência de FR, assim como observação clínica de sinais e sintomas que sugiram esse efeito colateral.

Descritores: Cefaleia, Cefaleia em salvas, Fibrose retroperitoneal.

INTRODUCTION

Chronic migraine affects approximately 2% of the world population¹. It impairs patients' quality of life (QL) and results in major losses for society. In the United States, direct and indirect migraine costs are estimated in more than 20 billion dollars per year².

Diagnostic criteria for chronic migraine, reviewed in 2006 are³: a) headache more than once or twice a month, for at least three months; b) patient has at least five headache attacks meeting the criteria of migraine without aura; c) headache eight or more days per month for at least three months meeting c1 and/or c2 criteria, such as: c1a) headache with at least two of the following characteristics: unilateral, pulsatile, severe to moderate, triggered or worsened by routine activities; c1b) at least one characteristic during pain crisis: nausea and/or vomiting photophobia and phonophobia; c2) treated or relieved by triptans or ergot before the onset of migraine-related symptoms; and d) no drug abuse and headache not attributed to other causes.

Treatment of both chronic and episodic migraine may be divided into abortive (in the acute phase) and preventive (as prophylaxis). According to the Consensus of the Brazilian Headache Society⁴ and to the Guidelines of the American Consortium for Headache⁵, preventive migraine treatment is indicated in the following cir-

stances: recurrent migraine interfering with patients' routine in spite of treatment during the acute phase; frequent pain crises; contraindication, failure, poor tolerance or abuse of abortive drugs; special migraine subtypes (hemiplegic, basilar, with prolonged aura, with frequent and atypical aura and migrainous infarction).

Drugs for migraine prevention are⁶: a) first line: beta-blockers (atenolol and propranolol), tricyclic antidepressants (amitriptyline and nortriptyline) and calcium channel blockers (flunarizine); b) second line: anti-epileptics (valproic acid and topiramate); c) third line: methysergide and pizotifen and d) fourth line: chlorpromazine and quetiapine.

Another chronic headache of major clinical importance due to its high morbidity is cluster headache. It is considered so disabling that some patients even attempt to commit suicide if the disease is not effectively managed⁷. Similar to migraine, this is a primary headache, however of short duration and associated to autonomic activation. According to the Headache Classification Subcommittee of the International Headache Society, cluster headache diagnostic criteria are⁸: a) at least five attacks meeting criteria from b to d; b) severe unilateral, orbital supraorbital and/or temporal pain lasting from 15 to 180 minutes if not treated; c) presence of at least one autonomic symptom at pain site: conjunctival injection, tearing, nasal congestion, rhinorrhea, ptosis, eyelid edema, miosis or forehead sweating; and d) frequency from one episode in alternate days to eight episodes per day. In its chronic form, attacks occur for more than one year without remission or with a remission period shorter than 14 days.

Episodic and chronic cluster headaches are similarly treated. Subcutaneous sumatriptan and inhalational oxygen are first line treatment for cluster headache. Other drugs with some evidence of efficacy are ergot, lidocaine and octetide^{7,9}. The prophylactic treatment should start as early as possible, since patients have typically one to eight daily pain attacks and repeated abortive drugs could imply toxicity. Verapamil is the preventive treatment of choice for cluster headaches. Other effective options are glucocorticoids, lithium, topiramate and methysergide^{7,9}. So, methysergide (1-methyllysergic acid butanolamide) is a drug used to prevent both migraine and cluster headaches. This is a semi-synthetic ergot alkaloid similar in structure to methylergonovine. It is 5HT₂ receptor antagonist and agonist of some 5HT₁ sub-types (5HT_{1D} present in blood and cranial vessels; 5HT_{1B} present in trigeminal nerve terminations)¹⁰⁻¹². Methysergide acts both directly and through its active metabolite, methylergonovine or methylergometrine, which is probably the

substance responsible for its prolonged anti-migraine effect. Its oral bioavailability is approximately 13% as a function of its fast conversion to methylergometrine. Methysergide and methylergometrine half-life is 60 and 220 minutes, respectively^{11,13}. Methylergometrine has also dopaminergic activity¹⁴.

Methysergide was the first drug used to preventively treat migraine. Between 1948 and 1953, serotonin, serum vasoconstrictor factor, was identified, isolated and synthesized. In the 1950s and 1960s, its association to migraine was progressively established by some studies^{10,11,15-17}. The search for some serotonin receptors antagonist with good tolerability has led to the synthesis of methysergide, which was introduced in the clinical practice in 1959 by Italian neurologist Federigo Sicuteri, from the Department of Clinical Pharmacology, University of Florence¹⁸. In line with Wolff, he also stated that local release of substances such as serotonin, histamine, bradykinin, among others, would lead to increased arterial tone, participating on the pathophysiology of some chronic headaches, such as migraine and cluster headache.

Since then, several studies indicating methysergide to prevent migraine and cluster headache were developed, showing the effectiveness of this drug¹⁹⁻²².

Approximately 20% to 45% of patients experience methysergide side-effects and approximately 10% of them discontinue its use. Most common side-effects, present in more than 5% of patients are sleepiness, nausea, vomiting, weight gain, epigastric pain, psychiatric disorders, peripheral arterial insufficiency and peripheral edema. In 24% to 35% of cases, symptoms are developed when the dose is higher than 8 mg/day¹¹. Although uncommon, fibrosis is the most feared side-effect. Its incidence was estimated in 1% by a study²³, differently from the incidence posteriorly found of 1/5000¹¹.

This study aimed at reporting two cases of primary chronic headache (1 patient with migraine and one patient with cluster headache), refractory to first line drugs, who obtained an adequate control after using methysergide, which was withdrawn due to suspicion of retroperitoneal fibrosis (RF).

CASE REPORTS

Case 1: Female patient, 69 years old, diagnosed with chronic and difficult to treat migraine since her 15 years of age. She had already used propranolol, amitriptyline, nortriptyline, valproic acid and topiramate. Methysergide (1 mg/day) was started with satisfactory migraine control. After 24 months of continuous me-

thysergide use, painless asymmetric lower limbs edema, more severe to the left, was observed. Lower limbs duplex scan was normal. Abdominal ultrasound (US) could not show the iliac vein and the possibility of retroperitoneal fibrosis was raised. Abdominal CT was also normal. In spite of negative RF screening, persistence of clinical signs has encouraged methysergide withdrawal. There has been total lower limbs edema resolution one week after drug withdrawal.

Case 2: Male patient, 58 years old, with episodic cluster headache poorly controlled with first line drugs. Methysergide (1 mg) at every 12 hours was started, with adequate control of cluster headache attacks and with patient reporting significant QL improvement after the introduction of the drug. After 30 months of continuous use, he complained of diffuse abdominal pain irradiating to left testicular region, in addition to sexual dysfunction with complaint of “dry” orgasm and symmetric lower limbs edema. At investigation, lower limbs duplex scan, abdominal US and spermogram were normal. Similar to case 1, in spite of negative RF screening, signs and symptoms were progressing, which has encouraged methysergide withdrawal two months after initial patient's complaints. Seven days after methysergide dose decrease to 1 mg/day, clinical changes were totally resolved.

DISCUSSION

RF is an uncommon, insidious and nonspecific disease, thus being difficult to treat. Approximately 2/3 of cases are idiopathic. Most common secondary causes are drugs, retroperitoneal infections, aortic aneurysm and neoplasias²⁴. It is more prevalent among males, except when its etiology is related to prolonged methysergide use, when it becomes more frequent among females²⁵. Most common early symptom is pain, which may be abdominal, lumbar, clamping, continuous and not exacerbated by movement or palpation. Pain characteristics tend to change if the ureter is involved, for example. Lower limbs edema, probably secondary to extrinsic lymphatic and venous system compression, is also a common sign, as well as the presence of deep vein thrombosis. Scrotal edema, varicocele and hydrocele are also very frequent consequences, possibly secondary to the involvement of gonadal vessels. Less common symptoms, and in general associated to more advanced cases are: dysuria, oliguria, uremia-related complaints, lameness and intestinal ischemia^{26,27}.

Imaging exams are critical for RF diagnosis and handling and may even, in some situations, differentiate secondary from idiopathic cases. Abdominal US is in

general the first exam for being more accessible and for easily showing urinary tract changes, which is the region most earlier affected by RF. However, CT with contrasts is the exam of choice, since it defines fibrosis extension and helps identifying secondary causes. MRI is equally valuable with the advantage of not needing contrast. CT and MRI are important to define fibrosis extension and to show simultaneous changes which may suggest secondary causes^{26,28}.

Fibrosis was firstly associated to methysergide in 1965^{10,29}. Authors have described three RF cases in patients under methysergide. There has been no direct causal relationship between methysergide and RF in these patients, but no other cause for such change was found. Since findings were insufficient to support drug withdrawal, authors proposed the discontinuation of the drug for three months at every year of regular use, in addition to periodic renal function and uremia follow up.

One year later, a study²³ with 27 RF cases, 14 of them with diagnosis confirmed by biopsy and 13 of them by additional workup which has identified variable treatment duration from 9 to 54 months and doses from 2 to 28 mg¹⁰. The incidence of pleural and cardiac RF is 1:5000 patients treated with methysergide¹¹. It decreases with drug withdrawal. Studies^{11,30} have evaluated drug withdrawal for four weeks at every year of use and have observed reduction of cases of fibrosis. No case was observed with its periodic withdrawal. Current orientation is to give an interval of 4 to 8 weeks at every six months of use, in addition to periodic exams and renal function to be able to diagnose early RF cases.

CONCLUSION

Methysergide is effective for patients with headache refractory to first line drugs; however its chronic use should be done with caution, always valuing signs and symptoms suggesting early RF symptoms.

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