

## Phenytoin in the Treatment of Osmophobia in Migraine Patient: A Case Report

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### Abstract

**Background:** Osmophobia is defined as intolerance to odors and it is associated to primary headaches, particularly to migraine with or without aura. It occurs during headache attacks and/or in the period between headache attacks. It is not yet known specific treatment for osmophobia.

**Case:** We describe a case of a 38-year-old woman diagnosed with migraine without aura according to ICHD-3 criteria. She complained of severe osmophobia both during and between headache attacks. In the pain-free period, she had extreme intolerance to any odors. Physical examination and imaging were unremarkable. Several prophylactic treatments of migraine were administered the past two years. There was a marked improvement in the frequency and intensity of headache attacks, but osmophobia remained unchanged. She would like to treat only her osmophobia. A prophylactic treatment with phenytoin was started to osmophobia, with disappearance of this symptom within 90 days.

**Conclusion:** From our experience in this case, phenytoin should be considered as possible prophylactic treatment for osmophobia between headache attacks in migraine patients.

**Keywords:** Migraine; Osmophobia; Osmophobia diary; Treatment; Phenytoin

### Introduction

There is a significant association between odors and primary headaches, particularly to migraine with or without aura [1-6] and tension-type headache [1,6-8]. The literature of its occurrence in secondary headaches is very scarce [9]. They are triggers of headache attacks [2,10] or intolerance factor (osmophobia) [1] both during and between headache attacks (pain-free period) [1,3,11,12].

In migraine patients, prevalence of osmophobia during the headache attacks ranges from 20.0% to 81.7% [1,3,5,6,8,13] and in the period between headache attacks, this prevalence ranges from 24.0% to 53.3% [1,3,11,12]. Several categories of drugs are used in migraine prophylaxis, such as beta-adrenergic blockers, tricyclic antidepressants, calcium channel blockers, serotonergic antagonist, antiepileptics, and others [14-16]. All of these drugs are effective in controlling pain, but without action in osmophobia. However, phenytoin, an antiepileptic drug not used in migraine prophylaxis, has been suggested to treat the central and autonomic disturbances of migraine, such as osmophobia, hyperosmia, pain in the limbs and motion sickness that occur in the pain-free period [17].

We report a case of osmophobia between headache attacks in a migraine patient who was successfully treated with phenytoin. It is not yet known any specific treatment for osmophobia, and to the best of our knowledge, this is the first description of phenytoin in the treatment of osmophobia between headache attacks in a migraine patient.

### Case Report

A 38-year-old woman was seen in our headache clinic with a 12-year history of headaches that fulfilled all the diagnostic criteria for migraine without aura. Headache attacks were described as pulsating, localized to the right front temporal region, at a frequency of 1-2 episodes per month, mild to moderate intensity, and lasting 4-72 hours. The pain was exacerbated by routine physical activity. During headache attacks, nausea and/or vomiting, photophobia, phonophobia and osmophobia were present. There were no cranial autonomic symptoms, such as lacrimation, conjunctival injection, nasal congestion, rhinorrhea, forehead/facial sweating, ptosis or miosis. She complained of severe

osmophobia both during and between headache attacks. In the pain-free period, she had extreme intolerance to any odors. She could not approach odorants, such as perfumes, cleaning products, paints, pesticides, cigarette smoke, etc. Odors triggered nausea. Her general medical and neurological examinations were normal. Brain MRI and CT were normal. Routine blood tests (biochemical, haematological, liver, kidney and metabolic investigations) yielded normal results. Migraine prophylaxis had been administered daily for the past two years. The drugs used were beta-adrenergic blockers, tricyclic antidepressants, calcium channel blockers, serotonergic antagonist and antiepileptics, isolated or in association. There was a marked improvement in the frequency and intensity of headache attacks, but osmophobia remained unchanged. According to the patient, osmophobia caused great impact on her quality of life, more than headache. She would like to treat only her osmophobia. A prophylactic treatment with phenytoin was started to osmophobia, at a dose of 100 mg, once a day. Her improvement was accompanied through an osmophobia diary which was filled out by patient herself during the treatment period. There was a reduction in the frequency and intensity of osmophobia in the first two months of treatment, with disappearance of this symptom within 90 days, as shown in Table 1. Phenytoin was maintained for another three months. The patient remained without osmophobia for the following two years.

### Discussion

Our patient met the diagnostic criteria for migraine without aura, according to International Classification of Headache Disorders, third edition, beta version (ICHD-3β) [18], but her main complaint was a

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Time (days)	Frequency (days/month)	Intensity				OI
		Mild (VAS 1-4)	Moderate (VAS 5-7)	Severe (VAS 8-9)	Very severe (VAS 10)	
1- 30	10	0	4	6	0	26
31-60	3	2	1	0	0	4
61-90	0	0	0	0	0	0

Legend: VAS-visual analog scale; OI-osmophobia index. To calculate the osmophobia index, we multiplied the amount of mild, moderate, severe and very severe intensities, respectively, by the scores 1, 2, 3 and 4.

**Table 1:** Distribution of the frequency and intensity of osmophobia between headache attacks for 90 days in a migraine patient.

NAME		INSTRUCTIONS FOR COMPLETING THE DIARY:																															
		Days with headache: mark with an 'X' the box corresponding to the day he/she felt pain;																															
		Days with osmophobia: mark with an 'X' the box corresponding to the day he/she felt intolerance to some smell (pleasant or unpleasant);																															
		Intensity of osmophobia: even if there are variations in the intensity of osmophobia, note only the highest intensity during the day;																															
		Total: at the end of each month, add the number of episodes of osmophobia and the number of times that these episodes were mild, moderate, severe or very severe																															
Month: January		Year: 2014																															
th headache		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Total
headache				X								X	X																				5
Days with osmophobia	X							X	X					X		X									X								7
Mild									X																								1x1=1
Moderate	X																																1x2=2
Severe									X								X									X							4x3=12
Very severe															X																		1x4=4
										Days with osmophobia		6	Osmophobia index		19																		

**Figure 1:** The reduction of this index indicates an improvement in the intensity of osmophobia.

severe osmophobia. Although osmophobia is not a diagnostic criterion for migraine, many studies show that this symptom is highly prevalent and is useful to differentiate migraine from tension-type headache [1,4,5,7,8,13]. Such as headache, osmophobia affects the quality of life of migraine patients and hinders the performance of their professional activities, especially in those who work in environments with strong odors, such as in perfumery, gas station and the selling of insecticide or beauty products [10,11]. Many drugs are used to prevent headache attacks [14-16], but unfortunately, there is no specific treatment for osmophobia. If a migraine patient is treated with prophylactic medications he will improve or become pain free [19], but osmophobia between headache attacks will remain (Table 1).

There is a study published in 1986 that suggests treating the central and autonomic disturbances of migraine that occur in the pain-free period, such as osmophobia, hyperosmia, limb pain and motion sickness. Phenytoin is suggested in the treatment of osmophobia [17]. Recently, a patient with osmophobia caused by partial hypopituitarism with isolated ACTH deficiency was treated with sertraline [20]. In our patient, osmophobia was treated with phenytoin at a dose of 100 mg, once a day. After 60 days of treatment, we observed a reduction in the frequency and intensity of osmophobia with disappearance of this symptom within 90 days. Phenytoin was maintained for three months after the patient becoming asymptomatic. The patient remained without osmophobia for the following two years. The improvement of patient was accompanied through an osmophobia diary [11], which is an important diagnostic tool for the evaluation of all characteristics inherent in osmophobia, such as association with headache, frequency and intensity. In this diary, it is used a visual analog scale (VAS) to classify the intensity of osmophobia as VAS 1-4 (mild), VAS 5-7

(moderate), VAS 8-9 (severe), and VAS 10 (very severe).

During the follow-up of this patient, scores 1, 2, 3 and 4 were assigned, respectively, for mild, moderate, severe and very severe intensities during the treatment period with phenytoin. Then we multiplied the four intensity groups by its respective scores and the sum of these products was called osmophobia index (OI). The reduction of this index indicates an improvement in the intensity of osmophobia (Figure 1).

Phenytoin is an antiepileptic drug that was synthesized for the first time in 1908 by Heinrich Biltz [21] and since 1938 it is used primarily for controlling partial seizures, tonic-clonic or clonic-generalized [22]. However, it is also used to treat idiopathic trigeminal neuralgia and vestibular paroxysmia [23]. The risks of its long-term use include gingival hypertrophy [24] and cognitive changes [25]. Gingival hypertrophy is a major side effects associated with the administration of phenytoin. The mechanism by which phenytoin induces gingival hypertrophy is not well understood but we know that plasma phenytoin level and long-term use appear to be a risk factor for the appearance of this adverse effect [26]. In our patient, phenytoin was administered in a low dose (100 mg/day) and a short-term use of six months. In epilepsy control, phenytoin acts by blocking sodium channels, but in preventing osmophobia its mechanism is unknown. We hypothesize that odorant substances bind to olfactory receptors and activate adenylate cyclase, leading to cyclic adenosine monophosphate (cAMP), which binds to sodium channels, triggering an action potential which propagates to the olfactory bulb [27]. These electrical impulses are directed to the primary olfactory cortex, where discrimination of odor happens [3,10]. Therefore, the action potential is not spread when the sodium channels

are blocked by phenytoin and osmophobia is relieved. We suggest that all migraine patients who present osmophobia between headache attacks be exposed to phenytoin in order to determine if they are able to become asymptomatic.

## Conclusions

From our experience in this case, phenytoin should be considered as possible prophylactic treatment for osmophobia between headache attacks in migraine patients.

## Clinical Implications

- Such as headache, osmophobia affects the quality of life of migraine patients.

Osmophobia between headache attacks may be treated with phenytoin.

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