Journal of the Neurological Sciences 382 (2017) 36–39

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Negative myoclonus induced by gabapentin and pregabalin: A case series and systematic literature review

Jung Bin Kim[a], Jin-Man Jung[b], Moon-Ho Park[b], Eun Ju Lee[c], Do-Young Kwon[b,*]

[a] Department of Neurology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea
[b] Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, South Korea
[c] Medical Library, Korea University, Seoul, South Korea

ARTICLE INFO

Keywords:
Negative myoclonus
Pregabalin
Gabapentin
Renal function
T-type calcium channel

ABSTRACT

Introduction: Negative myoclonus is a jerky, brief, and sudden interruption of voluntary muscle contraction. Although gabapentin and pregabalin have been reported to induce positive myoclonus in some patients with impaired renal function, there are only a few studies describing pregabalin- or gabapentin-induced negative myoclonus. This study reviewed patients who had developed pregabalin- or gabapentin-induced negative myoclonus.

Methods: We collected the patients with negative myoclonus who were referred to the department of neurology at a university-affiliated hospital and selected pregabalin- or gabapentin-induced negative myoclonus. Then reviewed the literature with respect to pregabalin- or gabapentin-induced negative myoclonus.

Results: A total of 77 patients with negative myoclonus were reviewed. Among them, 21 neuropathic pain patients who were prescribed and developed negative myoclonus induced by pregabalin (9 cases) or gabapentin (12 cases). To prove causality of the drug, probable and certain level of category according to the WHO-UMC criteria were recruited. Of the 21 patients, 3 had impaired renal function, while 18 had normal renal function. Review of the literature identified 7 further cases (6 had normal renal function) with pregabalin- or gabapentin-induced negative myoclonus.

Conclusion: Pregabalin- and gabapentin-induced negative myoclonus can develop even in patients with normal renal function. Physicians should keep in mind the possibility of patients developing negative myoclonus under treatment of pregabalin or gabapentin even in short period of time and with low dosage, and in the normal range of renal function. Further prospective study investigating incidence and risk factors is warranted.

1. Introduction

Negative myoclonus (NM) refers to a jerky, shock-like involuntary movement, due to a sudden interruption of voluntary muscle contraction. The concept was first introduced by Shahani and Young in an effort to characterize post-hypoxic intention myoclonus and asterixis [1]. At present, the term NM encompasses all involuntary movements of brief and spasmodic interruption of tonic muscle activities that can lead to a sudden postural lapse [2]. It has been suggested that NM may develop from the dysfunction of neural circuits responsible for the maintenance of sustained muscle contractions, such as lesions in the ventrolateral thalamus, or by a generalized neurochemical imbalance in metabolic encephalopathies [3].

Various drugs and toxic metabolic encephalopathies are known to cause acute-onset positive myoclonus. Among the drugs linked to the development of myoclonus, there have been several reports that demonstrated pregabalin- or gabapentin-induced positive myoclonus [4–10]. Indeed, an observational study showed that myoclonus had developed in 13 of 104 (12.5%) patients, with the occurrence of epilepsy among those taking gabapentin [10]. Moreover, it has been found that the possibility of developing pregabalin- or gabapentin-induced myoclonus in patients with impaired renal function is relatively high compared to patients with normal renal function [4,6,8,9]. Given that positive and negative myoclonus share common precipitating factors, it is plausible that pregabalin and gabapentin may be implicated in the development of NM. However, to the best of our current knowledge, there is a paucity of reports describing NM induced by pregabalin or gabapentin [11–14].

In addition, NM patients easily considered as having a tremor or weakness in clinic, which lead to underdiagnosis of those conditions and the incidence could be underestimated. We therefore aimed to identify the clinical characteristics of patients with pregabalin- or

* Corresponding author at: Department of Neurology, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, South Korea.
E-mail address: kwondoya@korea.ac.kr (D.-Y. Kwon).

http://dx.doi.org/10.1016/j.jns.2017.09.019
Received 27 June 2017; Received in revised form 11 September 2017; Accepted 14 September 2017
Available online 18 September 2017
0022-510X/

gabapentin-induced NM. To this end, we reviewed medical records of NM patients using registry data from the department of neurology at a university-affiliated medical center. We then reviewed the literature with respect to pregabalin- or gabapentin-induced negative myoclonus.

2. Materials and methods

This study is a retrospective review of prospectively-collected registry data. Using the hospital registry database, we reviewed the medical records of all patients who were referred to the department of neurology at university-affiliated hospital for NM (defined as a shock-like, involuntary jerky movement, due to a sudden and brief interruption of muscle activity) [2]. The NM registry data were collected for 4 years. Diagnosis of the NM was based on clinical features, such as sudden falls or dropping of objects due to interruption of muscle activity. Patients with NM were finally included in the registry after a confirmation through neurologic examination by a movement disorder specialist. According to the etiology of NM, all patients with NM were classified into physiologic, essential, epileptic, symptomatic, and psychogenic myoclonus [15,16]. Based on medical records, we further investigated the demographic and clinical data of patients with pregabalin- or gabapentin-induced NM. Cases of probable and certain level of World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories were enrolled, considering temporal relationship to drug intake and response to withdrawal. Response to rechallenge was proved, in some cases [17]. That is, all of the pregabalin- or gabapentin-induced NM was defined as the occurrence of NM after administration and the recovery of symptoms after withdrawal of the drugs. All patients with pregabalin- or gabapentin-induced NM had no evidence of acute lesions on brain MRI and epileptogenic conditions on electroencephalography. We collected data such as age at NM onset, duration of NM symptoms, comorbidities, and findings of serologic laboratory tests (*i.e.* blood urea nitrogen [BUN], creatinine, aspartate transaminase [AST], and alanine transaminase [ALT]). A literature search of PubMed was performed on March 29, 2017 using the search terms “Myoclonus OR Asterixis OR Flapping tremor AND Pregabalin OR Gabapentin OR Voltage dependent calcium channel”. The search was limited to articles in English. PubMed yielded 47 articles. A manual review of all 47 abstracts was then performed to exclude duplicate and irrelevant articles. In total, 6 articles were deemed relevant and accessible for our systematic review of pregabalin- or gabapentin-induced NM.

3. Results

A total of 77 patients with NM (mean age = 65.8; 7 females) were initially included in this study. The etiological classification of included NM patients is summarized in Table 1. The most common etiology of NM was found as symptomatic (62 cases; 80.5%), followed by undetermined (12 cases; 15.6%), psychogenic (2 cases; 2.6%), and epileptic (1 case; 1.3%).

Among the 62 symptomatic NM patients, the NM of 21 patients was found to be induced by pregabalin (9 cases) or gabapentin (12 cases). All of the 21 patients were prescribed pregabalin or gabapentin for the controlling of neuropathic pain. Of the 21 patients, 3 showed impairment of renal function (mean BUN = 58.1 mg/dl; mean creatinine = 7.0 mg/dl), while 18 had normal renal function (mean BUN = 16.3 mg/dl; mean creatinine = 1.0 mg/dl). Mean administration dosage of pregabalin and gabapentin was 217 mg/day and 400 mg/day, respectively. The mean time lapse until development of NM after administration of pregabalin or gabapentin was 3.5 days. Clinical data for patients with NM induced by pregabalin or gabapentin is described in Table 2.

Our literature search on pregabalin- or gabapentin-induced NM identified 5 reports of single cases and 1 report of 2 cases. Table 3 summarizes the reported cases of pregabalin- and gabapentin-induced NM. Pregabalin or gabapentin was administrated for controlling neuropathic pain in 6 cases and for controlling simple partial seizures in 1 case. Of the 7 cases, 2 had impaired renal function, while 5 had normal renal function.

Table 1
Classification of patients with negative myoclonus.

Classification	Number of cases (n = 77)
Symptomatic	
Infectious or post-infectious	
Herpes simplex encephalitis	1
Metabolic	
Hepatic failure	1
Renal failure[a]	14
Hypocalcemia	1
Toxic and drug-induced	
Pregabalin[a]	9
Gabapentin[a]	12
Alcohol	7
Other drugs (NSAIDs, antibiotics, codeine, tramadol etc.)	18
Focal nervous system lesion	
Post-stroke	2
Psychogenic	2
Epileptic	1
Undetermined	12

NSAIDs non-steroidal anti-inflammatory drugs.
[a] Two patients with gabapentin-induced and one patient with pregabalin-induced negative myoclonus also had renal failure.

4. Discussion

Our review demonstrated that pregabalin- or gabapentin-induced NM was the leading cause of NM in our study population. Almost all patients (18 of 21 cases, 85.7%) with NM induced by pregabalin or gabapentin were found to have normal renal function on serologic test. Moreover, the dose of the pregabalin or gabapentin was not considerably high, and the time lapse until development of NM after administration of those drugs was not very long. On the literature review, we found that only 7 patients with pregabalin- or gabapentin-induced NM were reported. Most of the previously reported pregabalin- or gabapentin-induced NM patients (5 out of 7) had normal renal function. In addition, NM was developed within 4 days after administration of pregabalin or gabapentin. These findings were very similar to those of our study population.

NM can be observed in a variety of clinical situations, such as encephalopathies associated with toxic and metabolic dysfunctions, as well as epileptogenic conditions. It has been relatively well-known that positive myoclonus could be induced by pregabalin or gabapentin, whereas there have been only a few reports describing pregabalin- or gabapentin-induced NM [11–14,18,19]. Therefore, the pathophysiological mechanisms that underlie the development of NM induced by pregabalin or gabapentin remain unknown. In addition, unlike positive myoclonus, NM may easily misdiagnose as having a tremor or weakness in clinic which lead to underestimation of their incidence. With regard to positive myoclonus, the involvement of the serotonin neurotransmitter system has been suggested as the mechanism responsible for the development of myoclonus [10]. In addition, most cases of pregabalin- or gabapentin-induced myoclonus were observed in patients with impaired renal function; therefore, drug intoxication due to impaired renal excretion was proposed as a possible underlying mechanism in the development of myoclonus [4,6]. However, a different study suggested that pregabalin-induced myoclonus seemed to depend on a threshold effect rather than a linear dose dependency [20], suggesting an effect of the pregabalin *per se* in the development of myoclonus. Our findings also suggest that effects of pregabalin or gabapentin *per se* may play an important role in development of NM for the following reasons: 1)