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Original Article

Gabapentin therapy in patients with orofacial neuropathic pain: Report of 12 cases

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ABSTRACT

Objective: There are several types of orofacial neuropathic pain and some of these types are often refractory to treatment. Gabapentin is an oral antiepileptic agent with a proven analgesic effect in various traumatic neuropathic pain syndromes. We retrospectively examined the analgesic effect of gabapentin on non-dental and non-traumatic orofacial neuropathic pain.
Subjects and methods: This study included 12 patients. All patients showed an excessive response to noxious (hyperalgesia) and/or innocuous (allodynia) stimuli in the affected region. Gabapentin therapy was initiated with a dosage of 200–600 mg/day. Pain intensity was assessed using a modified numerical rating scale (m-NRS) (0, no pain; 10, pain equal to that experienced on the day gabapentin therapy was initiated). In addition, the side effects were also recorded.
Results: All the patients had received medications for their pain prior to referral, but the drugs failed to provide adequate relief from their neuropathic pain. The m-NRS scores for all patients started decreasing within 7 days after internal use was initiated. The average time taken for the m-NRS score to decrease to half was 3.3 (1.7) days. Side effects were observed in 2 patients.
Conclusion: We concluded that gabapentin therapy is efficacious for the treatment of orofacial neuropathic pain in selected patients.

1. Introduction

Neuropathic pain has been defined by the International Association for the Study of Pain as pain was initiated or caused by a primary lesion or dysfunction in the nervous system [1] There are several types of orofacial neuropathic pain, for example, stabbing pain, shooting pain, and continuous dull pain; some of these types are often refractory to treatment.

Gabapentin is an oral antiepileptic agent with an unknown mechanism of action and has already been used in some countries for neuropathic pain [2–4]. Gabapentin was approved as an antiepileptic agent in Japan in September 2006. Because gabapentin is an anticonvulsant with a proven analgesic effect in various traumatic neuropathic pain syndromes, we used this drug for treating non-dental and non-traumatic orofacial neuropathic pain, excluding psychophysiologic disorders. We retrospectively evaluated the efficacy and side effects of gabapentin therapy for orofacial neuropathic pain.

2. Patients and methods

This study included 12 patients who had been referred to Fukuoka University Hospital for orofacial pain in a wide range of areas. We could not diagnose idiopathic cranial neuralgias because the pain site was different from the nerve controlled site or had a long duration; therefore, we decided to aim for cases considered as having peripheral neuropathic pain. All the patients had failed to obtain relief from pain with previous pharmacologic interventions.

Gabapentin therapy was initiated with a dosage of 200–600 mg/day. For those patients who were unsteady while walking or used a stick, 200 mg/day was initiated before sleeping and the dosage was increased while confirming that there was no change in their walking condition as a result of the drug administration. For those patients who were relatively healthy with no walking problem, 600 mg/day (3 times after each meal) was administered in accordance with the administration method for epilepsy treatment. The dosage was increased every 7th day in order to relieve pain. Pain intensity was assessed using a modified numerical rating scale (m-NRS) (m-NRS scores: 0, no pain; 10, pain equal to that experienced on the day gabapentin therapy was initiated). The period during which the analgesic effect of gabapentin became apparent corresponded to the period when the m-NRS score started to decrease and we thus, determined the

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time at which the m-NRS score reduced to half the initial score. In addition, the side effects were also recorded.

3. Results

This study included 12 patients (women, 8; men, 4; age, 62.6 ± 14.7 years). Of these patients, 4 had cervicofacial pain; 3, mandibular gingival pain; 3, glossopharyngeal nerve pain; and 2, tongue margin pain.

Neuropathic pain presented as continuous stabbing pain in 5 patients, shooting pain in 9 patients, and continuous burning pain in 4 patients (some patients experienced more than one type of pain). All patients showed an excessive response to noxious (hyperalgesia) and/or innocuous (allodynia) stimuli in the affected region (Table 1). All the patients had received medications [nonsteroidal anti-inflammatory drugs (NSAIDs) and/or carbamazepine] for their pain prior to referral, but the drugs failed to provide adequate relief from their neuropathic symptoms (Table 2).

The m-NRS scores for all patients started decreasing within 7 days after internal use was initiated. The average time taken for the m-NRS score to decrease to half was 3.3 ± 1.7 days (Table 2).

The follow-up period ranged from 5 to 19 months, during which the median pain level decreased to 0/10; however, 2 patients withdrew from gabapentin therapy because of side effects. One of the side effects was skin symptoms (slight redness of the brow) and the other one was dizziness. One patient started to experience skin symptoms after 13 days of gabapentin administration, and this disappeared in 2 days after the discontinuation of the drug use. In another case, a patient complained of dizziness, 4 days after the start of the gabapentin administration, and had a remission of the symptom immediately after the cessation. However, severe side effects were not seen in any of our patients.

4. Discussion

The term “neuropathic pain” is used for pain syndromes for which the sustaining mechanisms are presumed to be related to aberrant somatosensory processes in the peripheral nervous system, central nervous system, or in both [5]. Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system. Neuropathic pain cannot be explained by a single disease process or a single specific location of damage. Common types of pain include burning, stabbing, numbness, and shooting. Almost all of our patients had pain on peripheral nerves of the face and neck. And then, we diagnosed the patients as having “neuropathic pain.”

Gabapentin was designed as a structural analog of γ-aminobutyric acid (GABA) but does not act on any known receptors in the brain, including GABA receptors [6]. Unlike other antiepileptic drugs, the receptor activity profile of gabapentin has not yet been determined, which supports the hypothesis that it has a novel mechanism of action [2]. Several studies have reported that gabapentin is effective in the treatment of postradical neck pain syndrome, postherpetic neuralgia, and postsurgical facial pain [3,4]. We examined the analgesic effect of gabapentin on non-dental and non-traumatic orofacial trigeminal neuropathic pain.

Tricyclic antidepressants and anticonvulsant drugs are often the first-line drugs to be selected for alleviating orofacial trigeminal neuropathic pain (first-line pharmacological treatment). Anticonvulsant drugs such as carbamazepine remain the best option for treating trigeminal neuralgia; glossopharyngeal neuralgia is also still treated using these drugs. Although anticonvulsant drugs are effective in reducing pain in several neuropathic pain disorders, treatment may be compromised and outweighed by their side effects. Current clinical treatments for neuropathic pain include

Table 1
Clinical characteristics of the subjects.

Case number	Age (gender)	Underlying disease	Site of pain	Somatosensory abnormality	Type of pain	Symptom duration
1	66 (F)	Rheumatic polyarthritis, diabetes Rheumatic aortitis	Posterior auricular area, left Orbital region, posterior neck skin	Hyperalgesia	Stabbing Shooting	5 days
2	32 (F)		Facial skin, oral mucosa	Hyperalgesia	Burning Stabbing	6 months
3	55 (F)	Multiple sclerosis	Posterior auricular area Facial and posterior neck skin,	Hyperalgesia	Stabbing Burning	24 months
4	79 (M)	Prostatauxe, arrhythmia Hypertension	Left temporal region	Allodynia Hyperalgesia	Stabbing	6 months
5	78 (F)	Hypertension	Bilateral gingiva of the mandible	Hyperalgesia	Stabbing Shooting	3 days
6	69 (F)	Terminal renal failure (hemodialysis)	Bilateral gingiva of the mandible	Hyperalgesia	Shooting	3 months
7	68 (M)	Spinocerebellar degeneration	Gingiva of the mandible Mandibular residual teeth	Allodynia Hyperalgesia	Shooting	3 months
8	74 (M)	Hypertension	Margin of the tongue Buccal mucosa	Allodynia Hyperalgesia	Burning Shooting	18 months
9	48 (48)		Margin of the tongue Dorsum of the tongue	Allodynia, Hyperalgesia	Burning Shooting	18 months
10	74 (M)	Hypertension, diabetes	Posterior part of tongue, buccal mucosa	Hyperalgesia	Shooting	24 months
11	45 (F)	Hypertension, diabetes	Posterior part of tongue	Allodynia, Hyperalgesia	Shooting	2 months
12	63 (F)	Terminal renal failure (hemodialysis)	Posterior part of tongue	Hyperalgesia	Shooting	24 months

NSAIDs, non-steroidal anti-inflammatory drugs; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors.

Table 2
Previous treatment for the orofacial pain and results of gabapentin therapy.

Case number	Previous treatment	Effective daily gabapentin dose (mg/day)	Days for m-NRS <5 (days)	Follow-up time (months)	Side effect
1	NSAIDs	800	3	7	
2	Amitriptyline	1200	4	6	
3	Carbamazepine	300	2	16	
4	NSAIDs, carbamazepine	200	4	5	
5	NSAIDs	400	2	13	
6		200	2	Stop	Dizziness
7	NSAIDs, carbamazepine	600	5	Stop	Slight redness of the brow
8	SNRI	1200	4	9	
9	Antianxiety drugs	900	3	9	
10	NSAIDs, carbamazepine	700	2	7	
11	Carbamazepine, SSRI	1200	5	19	
12	Carbamazepine	200	2	18	

m-NRS, modified numerical rating scale. Scores: 0, no pain; 10, pain equal to that experienced on the day gabapentin therapy was initiated.

amitriptyline, a tricyclic antidepressant that has mixed pharmacology and is clinically reported to impair cognitive performance, and gabapentin, a compound that selectively interacts with α-2 δ-1 calcium-channel subunits. The rapid entry of calcium into cells through activation of voltage-gated calcium channels directly affects membrane potential and contributes to electrical excitability. At presynaptic nerve terminals, calcium entry is the initial trigger mediating the release of neurotransmitters via the calcium-dependent fusion of synaptic vesicles and involves interactions with the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor complex of synaptic release proteins. Physiological factors or drugs that affect either presynaptic calcium channel activity have consequences on synaptic transmission, including mediating pain signaling. The N-type calcium channel exhibits a number of characteristics that make it a target for therapeutic intervention concerning chronic and neuropathic pain conditions [7]. Its exact mechanism of action is unknown, but gabapentin is thought to bind to the calcium channel in the central nervous system.

The common side effects of tricyclic antidepressants are mostly due to their anticholinergic activity and include dry mouth, drowsiness, nausea, dizziness, urinary retention, arrhythmias, and hepatic toxicity. Gabapentin is emerging as a first-line treatment for neuropathic pain in patients with a history of cardiovascular disorders, glaucoma, and urine retention [8,9]. Carbamazepine is not recommended for neuropathic pain other than trigeminal neuralgia because of the side effects. Often, the required multidrug therapy results in more side effects and drug interactions [10]. Drug interactions should be considered in the case of patients who regularly use medicines for underlying disease. Antiepileptic drugs have a favorable safety profile with minimal concerns regarding drug interactions and show no interference with hepatic enzymes.

The most common side effects of antiepileptic agents are dizziness and somnolence. The side effects were observed in 2 patients (13.3%) in our study. One of the side effects was dizziness and the other was slight redness of the brow. Because the effects appeared with a comparatively low starting dose, the appearance of side effects could be controlled, and in other reports as well [4].

All our patients experienced adequate relief from their severe pain during gabapentin therapy, and the analgesic effect of gabapentin was obtained as early as 3.3 days after initiation of therapy in this study. Because there were only few side effects related to gabapentin therapy and an analgesic effect was obtained at an earlier stage than with tricyclic antidepressants, we think that gabapentin is more effective than tricyclic antidepressants in treating orofacial neuropathic pain.

Of our 12 patients, 2 had pain for less than 1 month at the time of initial evaluation, suggesting that spontaneous recovery rather than efficacy of gabapentin therapy might have been responsible for the favorable outcome in these cases. However, this possibility is unlikely as they experienced recurrence of pain after discontinuation of gabapentin therapy.

We conclude that gabapentin therapy is efficacious for the treatment of orofacial neuropathic pain in selected patients.

Conflict of interest

The authors state they have no conflicts of interest.

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