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Concomitant Pregabalin and Tramadol Hydrochloride/Acetaminophen Formulation Relieved Neuropathic Itch of Gingiva: A Case Report

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Abstract: *Neuropathic itch of the gingiva is seldom seen in clinical situations, and most clinicians, including dental practitioners, do not have a way to deal with this condition. We report a case of neuropathic itch of gingiva that was successfully treated with concomitant pregabalin (50 mg 2×/day) and tramadol hydrochloride/acetaminophen (T/A: 37.5 mg/325 mg 1×/day) formulation. The 57-year-old Japanese female patient visited our hospital due to an itchy sensation of the right lower gingiva. The concomitant pregabalin and T/A formulation remarkably relieved the patient's itch; her score on a visual analogue scale representing itchy intensity was remarkably decreased at 2 weeks after the treatment initiation. The concomitant medication also improved her health-related quality of life (HRQoL) scores based on the Japanese version of the Short-Form 8 (SF-8) health survey. Significant adverse events did not occur. This concomitant medication may thus be useful for the treatment of neuropathic itch of gingiva.*

Keywords: *Pregabalin, Tramadol hydrochloride, Acetaminophen, Neuropathic itch, Gingiva*

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I. Introduction

The etiopathology of neuropathic itch remains still unclear, and neuropathic itch of the gingiva is seldom seen in clinical situations. Most clinicians, including dental practitioners, do not have a way to deal with this condition. We report a case of neuropathic itch of gingiva that was successfully treated with a concomitant pregabalin and tramadol hydrochloride/acetaminophen (T/A) formulation.

II. Case report

The patient was a 57-year-old Japanese female who visited the Department of Oral Medicine, Tokushima University Hospital due to an itchy sensation at her right lower gingiva. She was not on medication. Her medical history was taken, and we performed an oral examination, panoramic x-ray radiography, blood examination, culture, salivation test, somatosensory examinations, and quantitative sensory tests (QSTs). No abnormal findings were identified by these tests or in her medical history. Her pain sense was increased, but her tactile, cold, and warm senses were not lost. In the QSTs, the patient's tactile detection threshold was decreased, the two-point discrimination threshold was increased, and the cold and warm senses were lost. We diagnosed neuropathic itch of gingiva. Pregabalin (Lyrica®, Pfizer Japan, Tokyo) was administered at 50 mg twice daily, and increased to 100 mg (Fig. 1). T/A (Tramcet combination tablets, Janssen Pharmaceutical, Tokyo) formulation was concomitantly administered at 37.5 mg tramadol hydrochloride /325 mg acetaminophen once daily (Fig. 1).

The patient's response to this concomitant medication was evaluated using a visual analogue scale (VAS: 0-100 mm) representing itchy intensity [1]. The patient's VAS score decreased remarkably at 2 weeks after this concomitant medication was initiated (Fig. 1). We also assessed the patient's health-related quality of life (HRQoL) based on the Japanese-language version of the Short-Form 8 (SF-8) health survey, which is a miniature version of the Medical Outcome Study (MOS) 36-item short-form health survey ver. 2 (SF-36v2) and is a questionnaire used to measure the HRQoL in various diseases [2-4]. With respect to the subscales of the Japanese SF-8, physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE), and mental health (MH) were scored using norm-based methods (NBMs) that standardize the scores to a mean ± SD of 50 ± 10 as the Japanese average (2007), with higher scores indicating better health [5]. Regarding the

summary score of the Japanese SF-8, the physical component summary (PCS) and mental component summary (MCS) were also calculated by NBMs.

Our patient's BP, SF, MH, and MCS values increased from 38.2 to 52.5, from 37.7 to 45.6, from 36.3 to 50.7, and 33.4 to 46.3, respectively; her PF, GH, VT, and RE values did not change significantly (Table 1). The dosage of the concomitant pregabalin and T/A medication was subsequently tapered down. The patient accomplished the treatment goal without adverse events.

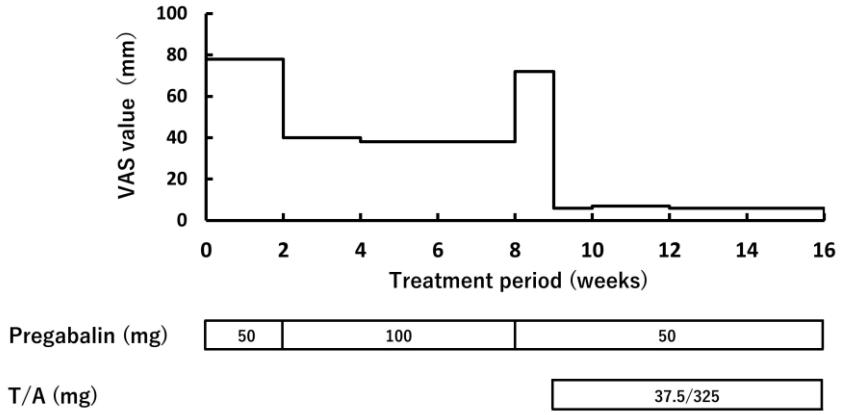

Fig. 1. Time course of the patient's VAS values regarding the intensity of itching of the gingiva and the dosages of pregabalin and T/A formulation. VAS, visual analogue scale; T/A, tramadol hydrochloride/acetaminophen.

Table 1 The score of the HRQoL[1] based on the Japanese SF-8[2]

Subscales	Before treatment	After treatment
PF[3]	53.5	53.5
RP[4]	54.1	47.4
BP[5]	38.2	52.5
GH[6]	40.4	40.4
VT[7]	44.5	44.5
SF[8]	37.7	45.6
RE[9]	48.0	48.0
MH[10]	36.3	50.7
PCS[11]	52.6	47.6
MCS[12]	33.4	46.3

[1]Health-related quality of life, [2]short-form 8 health survey, [3]physical functioning, [4]role limitations due to physical health, [5]bodily pain, [6]general health perceptions, [7]vitality, [8]social functioning, [9]role limitations due to emotional health, [10]mental health, [11]physical component summary, [12]mental component summary.

III. Discussion

To the best of our knowledge, this is the first case report of a concomitant pregabalin and T/A regimen relieving the neuropathic itching of gingiva and improving the patient's HRQoL based on the Japanese SF-8. Although the etiopathology of neuropathic itch is unclear, neuropathic itch is suspected to be due to dysfunction of the peripheral and central nervous systems [6,7]. Neuropathic itch follows peripheral nerve damage [8,9], and is induced independently of histamine [6], whereas, central sensitization develops and allodynia and hyperalgesia emerge [10]. In our patient's case, a right lower wisdom tooth was extracted > 3 months before the

concomitant pregabalin and T/A treatment. In addition, hyperalgesia was revealed by her somatosensory examinations. Neurophysiological examinations are often useful for the diagnosis of neuropathic itch [6].

Pregabalin is an anticonvulsant that has been used as a first-line treatment of neuropathic pain [11,12]. There are interactions between pain and itching [13]. Neuropathic itch occasionally parallels neuropathic pain [8,9]. In fact, pregabalin is reported to be effective against neuropathic itch [10]. Pregabalin, as an α2δ subunit of voltage-gated calcium channels, reduces the calcium reflux into nerve terminals and suppresses the release of presynaptic neurotransmitters such as glutamate, noradrenaline, and substance P [13,14]. Although the action mechanism of pregabalin in neuropathic itch is currently unclear, pregabalin may inhibit itching via a suppression of the release of presynaptic neurotransmitters. In fact, substance P can be a trigger of itching [15]. Pregabalin is also reported to inhibit a calcitonin gene-related peptide mediating itching [16].

Tramadol,which is a μ-opioid receptor agonist [17], inhibits serotonin-noradrenaline reuptake [17], and it is recommended as a second-line treatment for refractory pain [18]. Although the action mechanism of tramadol in neuropathic itch is not known, it may be similar to that for controlling pain. The μ-opioid receptor agonists can induce itching [7]. Morphine, which is a μ-opioid receptor agonist, induces histamine-dependent itch because morphine causes histamine to be released from mast cells [19]. Fortunately, tramadol did not induce further itching in our patient's case.

Regarding adverse events, pregabalin can cause dizziness, somnolence, peripheral edema, and dry mouth [13]. Tramadol can cause dizziness, constipation, drowsiness, nausea, and vomiting [14]. It is noteworthy that tramadol has a slight potential for abuse [18]. An overdose of acetaminophen can cause hepatic damage. The careful titration of doses and monitoring by laboratory tests are thus necessary to prevent adverse events.

The Japanese SF-8 consists of eight questions dealing with various ranges of physical or psychosocial aspects and is summarized physically or psychosocially. Itch diminishes the HRQoL [20-23], and is significantly associated with anxiety, depression, sleep disorder, and fatigue [24-29]. In our patient, her neuropathic itch also diminished her HRQoL. Psychosocial support should be considered for the treatment of neuropathic itch. The concomitant pregabalin and T/A medication had an inhibitory effect on the patient's neuropathic itch and helped to improve her HRQoL (Table 1). The Japanese SF-8 may be an effective tool for measuring the HRQoL of patients with neuropathic itch.

IV. Conclusion

Concomitant pregabalin and T/A formulation relieved neuropathic itch of the gingiva, and it may become a new therapeutic option for the treatment of neuropathic itch of gingiva.

Competing interests

The authors have no conflict of interests to declare regarding this study or the publication of this paper.

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