Duloxetine Plasma Concentrations and Its Effectiveness in the Treatment of Nonorganic Chronic Pain in the Orofacial Region

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Objective: The purpose of this study was to examine the relationship between the pain-relieving effects of duloxetine and its plasma concentrations in patients with burning mouth syndrome and atypical odontalgia characterized by chronic nonorganic pain in the orofacial region.

Methods: We administered duloxetine to 77 patients diagnosed as having burning mouth syndrome or atypical odontalgia for 12 weeks. The initial dose of duloxetine was established as 20 mg/d and was increased to 40 mg/d after week 2. We evaluated pain using the visual analog scale and depressive symptoms using the Structured Interview Guide for the Hamilton Depression Rating Scale at weeks 0, 2, 4, 6, 8, 10, and 12 and measured plasma concentrations of duloxetine 12 weeks after the start of its administration.

Results: Visual analog scale scores were significantly lower 12 weeks after than at the start of the administration of duloxetine (paired t test, t = 6.65, P < 0.0001). We examined the relationship between the rate of decreases in visual analog scale scores and plasma concentrations of duloxetine. There was no significant linear regression or quadratic regression.

Conclusions: Duloxetine significantly relieved pain in patients with chronic nonorganic pain in the orofacial region. However, no relationship was observed between its pain-relieving effects and plasma concentrations.

Key Words: atypical odontalgia, burning mouth syndrome (BMS), chronic pain, duloxetine, plasma concentration

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mirtazapine and its clinical effects on major depression.13 Regarding duloxetine, the relationship between its plasma concentrations and clinical effects on major depression was examined, and its plasma concentrations were found to be higher in patients with marked improvements in clinical global impressions than in those with moderate, minimal, or no improvements.14 However, to the best of our knowledge, there is currently no report to investigate a relationship between the pain-relieving effects of duloxetine and its plasma concentrations. Therefore, the purpose of this study was to clarify the relationship between the pain-relieving effects of duloxetine and its plasma concentrations in patients with chronic nonorganic pain in the orofacial region, namely, BMS or AO.

METHODS

We established a liaison psychiatry medical team consisting of dentists and psychiatrists in Aichi Gakuin University Dental Hospital in 1999. Psychiatrists and dentists in this team have cooperatively provided medical care for patients with chronic nonorganic pain in the orofacial region. Among all patients consulting our hospital for the first time, dental diagnoses were made by dentists, and psychiatric diagnoses were made by psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).15 Both diagnoses were recorded in medical records.16

The subjects participating in this study comprised 77 patients who consulted the Liaison Outpatient Clinic of Aichi Gakuin University Dental Hospital between April 2010 and March 2014 and were diagnosed as having BMS or AO by dentists and pain disorder by psychiatrists according to the DSM-IV-TR. Oof164 patients with BMS or AO, 87 patients were excluded based on the criteria described below or because of lack of informed consent. Written informed consent regarding study participation was obtained from all of the 77 subjects. No inducement/compensation was provided to patients to encourage them to participate. In order to make a psychiatric diagnosis based on the DSM-IV-TR, we used the Structured Clinical Interview for DSM-IV-Axis I Disorders.17 If necessary, radiography and blood test were conducted in addition to an oral examination, and, after confirming the absence of organic abnormalities, such as oral inflammation, a diagnosis of BMS or AO was reached. The subjects of this study included 41 of those who participated in the study conducted by Nagashima et al.18

The exclusion criteria were as follows: (1) a diagnosis of major depressive disorder on initial consultation, (2) a history of schizophrenia or other psychotic disorders or obvious current psychotic symptoms, (3) clinically overt dementia, (4) any serious somatic disorder, (5) previous use of duloxetine, and (6) use of any psychotropic agents within 2 weeks before study participation. In case of exclusion criterion 6, patients were allowed to enroll in the study if they discontinued drugs for 2 weeks. During this period, only the administration of alprazolam (up to 1.2 mg/d) and brotizolam (up to 0.5 mg/d) was allowed if necessary to relieve withdrawal symptoms.

The administration of duloxetine was initiated at 20 mg/d and was continued at 40 mg/d for 2 weeks or more after the start of its administration. However, the dose of duloxetine was allowed to be decreased to 20 mg/d for tolerability issues. Duloxetine was administered at bedtime once a day. Only alprazolam (up to 1.2 mg/d) and brotizolam (up to 0.5 mg/d) were permitted to be combined with duloxetine in order to manage anxiety or insomnia, which may develop after the administration of duloxetine.

In order to evaluate pain, we used the visual analog scale (VAS) before the administration of duloxetine (week 0) and after 2, 4, 6, 8, 10, and 12 weeks. Furthermore, we assessed depressive symptoms using the Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS) at weeks 0 and 12. In order to exclude the new onset of acute inflammation or organic disorders in the oral cavity, dentists conducted oral examinations at weeks 0, 2, 4, 6, 8, 10, and 12 to confirm the absence of organic abnormalities.

Blood was collected 12 weeks after the initiation of duloxetine administration in order to measure the plasma concentration of this drug; in all subjects, blood was collected 12 to 15 hours after the final dosing (before lunch the following day), and plasma-concentration measurements were conducted by Nemoto Science Co, Ltd. Duloxetine and duloxetine-d3 (internal standard [IS]) were purchased from TLC PharmaChem (Ontario, Canada), and high-performance liquid chromatography–grade acetonitrile and all other chemicals were purchased from Kanto Chemical (Tokyo, Japan). High-performance liquid chromatography was performed with an SIL-30ACMP auto sampler (Shimadzu, Kyoto, Japan) with LC-30AD pumps, a DGU-20A5R degasser, CTO-20AC column oven, and CBM-20A Lite system controller (Shimadzu). Separation was performed at 40°C with an analytical column, Inertsil ODS-SP (100 × 2.1-mm internal diameter, 5-μm particle size). The following solvents were used: 9:1 formic acid, acetonitrile, and the isocratic elution of 40% acetonitrile. The flow rate was 0.3 mL/min. The mass spectrometer was operated in the positive electrospray ionization mode using API 4000 Q TRAP (Applied Biosystems, Tokyo, Japan). Quantification was performed via multiple reaction monitoring of the transitions of m/z 298.064→153.900 for duloxetine and m/z 301.249→156.900 for IS, respectively. Data were acquired and processed using Analyst software (version 1.6.2). Approximately 10 mL of whole blood was collected in a Vacutainer tube containing heparin. The tube was immediately centrifuged at 1000g at 4°C for 5 minutes and stored at −29°C until used. The plasma sample (100 μL) was mixed with 10 μL of IS solution (1000 ng/mL) and 400 μL of acetonitrile. The mixture was left at −20°C for 20 minutes and then centrifuged at 12,000g at 4°C for 10 minutes. A 5-μL aliquot of the supernatant was injected into a liquid chromatography–tandem mass spectrometer. Stock and working standard solutions of duloxetine and stock and working IS solutions of duloxetine-d3 were prepared in methanol and stored at 4°C. The standard samples for calibration curves and quality control samples were prepared daily by spiking drug-free human plasma.

The protocol of this study was approved by the Ethical Committee of the School of Dentistry, Aichi-Gakuin University, and the Ethics Review Committee of Nagoya University Graduate School of Medicine (approval no. 372: Aichi-Gakuin University, approval no. 234: Nagoya University). This study was performed with sufficient consideration of the protection of personal information. This study was fully supported by a governmental grant of a Grant-in-Aid for Scientific Research (C, no. 24591703) and a governmental grant of a Grant-in-Aid for Young Scientists (B, no. 26860923) from the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Japanese Society for the Promotion of Science.

Statistical Analysis

Data are expressed as the mean (SD). A paired t test was used to compare VAS scores between weeks 0 and 12. In order to examine the influence of the presence or absence of depressive symptoms at the start of this study on serial changes in VAS scores, subjects were divided into 2 groups: groups with (initial HDRS score ≥8) and without (initial HDRS score ≤7) depressive symptoms, based on the HDRS score at the start of this study (initial HDRS score), according to our previous studies.19,20 A 2-way repeated-measures analysis of variance (ANOVA) was performed...
regarding depressive status and time as factors. A linear or quadratic regression analysis was conducted to investigate the relationship between plasma concentrations of duloxetine and the doses administered or VAS scores. \( P = 0.05 \) was regarded as significant. StatView version 5.0 (SAS Institute, Inc, Cary, NC) and SuperANOVA version 1.11 (Abacus Concepts, Inc, Berkeley, Calif) software were used for statistical analyses. A power analysis was performed using G*Power.\(^1\)

**RESULTS**

It was possible to perform blood collection and plasma-concentration measurements at week 12 in 49 of the 77 subjects tested. Twenty-eight patients dropped out for the following reasons: adverse reactions in 12 patients, insufficient effects (continuous therapy was refused) in 1, coming home in 1, family’s objection in 1, pain disappearance in 1, refusal related to anxiety regarding continuous therapy in 1, refusal of study participation in 1, refusal of continuous therapy in 1, refusal related to anxiety regarding continuous therapy in 1, and coming home in 1. The reasons for dropping out were unclear in 9 because they discontinued hospital visits.

All VAS and HDRS data were collected in 35 of these 49 patients. In 4 of 14 patients with data defects, VAS scores at week 0 or 12 were not adequately recorded, and thus, the rate of decreases in VAS scores was not able to be calculated (the rate of decreases in VAS scores = (the VAS score at 12 W – the VAS score at 0 W) / the VAS score at 0 W * –100). Furthermore, the plasma concentration of duloxetine was below the limit of quantitation in 1. Therefore, we excluded these 5 patients from subjects to be analyzed. The remaining 9 patients were included by adopting an intent-to-treat last-observation-carried-forward analysis. Forty-four subjects were ultimately analyzed.

The demographics of the 44 subjects at week 0, dental diagnoses, disease durations, initial HDRS scores, and final doses of duloxetine are presented in Table 1. Adverse reactions to duloxetine in the 77 study participants are shown in Table 2. The most frequent adverse reactions were nausea and constipation, which were observed in 12 patients (15.6%) and 9 patients (11.7%) respectively.

Visual analog scale scores before the administration of duloxetine and at week 12 are shown in Figure 1. The mean VAS score before the administration of duloxetine was 60.0 (SD, 26.6), whereas that at week 12 was 35.3 (SD, 27.8), showing a significant decrease (paired \( t \) test, \( t = 6.65, P < 0.0001 \); Fig. 1). In order to examine the influence of the presence or absence of depressive symptoms at the start of the administration of duloxetine on its pain-relieving effects, we divided patients into 2 groups: groups with (HDRS \( \geq 8 \)) and without (HDRS \( < 7 \)) depressive symptoms, based on HDRS scores at the initiation of the study, and compared serial changes in VAS scores between the 2 groups. A 2-way repeated-measures ANOVA revealed no significant interaction between time and the presence or absence of depressive symptoms at the start of this study (df = 6, \( F = 1.093, P = 0.37 \); Fig. 2), suggesting that pain improved through a similar course irrespective of initial depressive symptoms.

We evaluated the pain-relieving effects of duloxetine based on the rate of decreases in VAS scores and investigated the relationship between this rate and plasma concentrations of duloxetine. No significant linear regression (\( R^2 = 0.001, P = 0.88 \)) or quadratic regression (\( R^2 = 0.036, P = 0.47 \)) was observed between the 2 factors (Fig. 3). Furthermore, there was no significant linear

**TABLE 1.** Demographics, Dental Diagnoses, Disease Durations, Initial HDRS Scores, and Final Doses of Duloxetine Among Participants Included in This Study (n = 44)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5 (12.3)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male 4 (9.1) Female 40 (90.9)</td>
</tr>
<tr>
<td>Dental diagnosis, n (%)</td>
<td>BMS 29 (65.9) AO 15 (34.1)</td>
</tr>
<tr>
<td>Disease duration, mo</td>
<td>43.4 (67.9)</td>
</tr>
<tr>
<td>Initial HDRS score*</td>
<td>7.0 (6.7)</td>
</tr>
<tr>
<td>Final dose of duloxetine, mg/d</td>
<td>37.3 (6.9)</td>
</tr>
</tbody>
</table>

*Data are presented as the mean (SD).

**TABLE 2.** Adverse Events With Duloxetine in Included and Excluded Participants (n = 77)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12 (15.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (11.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9 (11.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Vomit</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Visual analog scale scores at the start of and after 12 weeks of the administration of duloxetine (n = 44). The mean VAS score before the start of duloxetine administration was 60.0 (SD, 26.6), whereas that at week 12 was 35.3 (SD, 27.8), showing a significant decrease (paired t test, \( t = 6.65, P < 0.0001 \)).
regression between the doses of duloxetine administered and its plasma concentrations ($R^2 = 0.048$, $P = 0.15$; Fig. 4).

In order to examine the relationship between the pain-relieving effects of duloxetine and its plasma concentrations, excluding patients in whom pain-relieving effects may not be obtained because of pharmacodynamic factors, such as polymorphisms at the drug action site (the dose of duloxetine was increased for this reason, leading to an elevation in its plasma concentration), we extracted/analyzed 30 patients with a VAS score improvement rating of 30% or greater, which was defined by Rowbotham\textsuperscript{19} as reflecting clinical pain-relieving effects. There was no significant linear regression ($R^2 = 0.023$, $P = 0.42$) or quadratic regression ($R^2 = 0.027$, $P = 0.69$) between the rate of decreases in VAS scores and plasma concentrations of duloxetine. In addition, we extracted/analyzed 20 patients with a VAS score improvement rating of 50% or greater, which was defined by Ko et al\textsuperscript{20} as reflecting pain-relieving effects. However, no relationship existed between the pain-relieving effects of duloxetine and its plasma concentrations.

According to a review on the effects of duloxetine on fibromyalgia or painful diabetic neuropathy,\textsuperscript{7} pain was relieved through its direct actions on pain rather than depression improvement–related secondary effects. We previously selected milnacipran\textsuperscript{9} or duloxetine\textsuperscript{10} to treat BMS or AO and indicated the pain-relieving effects of these agents. In addition, we reported that these effects were similar regardless of the presence or absence of depressive symptoms at the start of the study. These findings are consistent with the results of the present study.

A study involving the administration of amitriptyline to patients with postherpetic neuralgia showed that its pain-relieving effects were more prominent when its plasma concentration was higher.\textsuperscript{22} Furthermore, a dose-titration study using imipramine for patients with DNP demonstrated that its pain-relieving effects became more prominent with an increase in the plasma level of imipramine.\textsuperscript{23}

**FIGURE 2.** Serial changes in VAS scores with respect to the presence or absence of depressive symptoms at the start of this study (depressive patients: HDRS $\geq 8$, nondepressive patients: HDRS $\leq 7$, $n = 44$). A 2-way repeated-measures ANOVA revealed no significant interaction between time and initial presence or absence of depressive symptoms ($df = 6$, $F = 1.093$, $P = 0.37$).

**FIGURE 3.** Plasma concentrations of duloxetine and rate of decreases in VAS scores ($n = 44$). There was no significant linear regression ($R^2 = 0.001$, $P = 0.88$) or quadratic regression ($R^2 = 0.036$, $P = 0.47$) between plasma concentrations of duloxetine and the rate of decreases in VAS scores.

**DISCUSSION**

This is the first study to examine the relationship between the pain-relieving effects of duloxetine and its plasma concentrations in patients with chronic nonorganic pain in the orofacial region (dental diagnosis: BMS or AO, psychiatric diagnosis: pain disorder). We compared VAS scores before the administration of duloxetine and after 12 weeks, and a significant decrease was observed. Furthermore, pain improved through similar serial changes regardless of the presence or absence of depressive symptoms at the start of the study. We herein examined the relationship between the pain-relieving effects of duloxetine and its plasma concentrations and found no significant linear or quadratic regression between the 2 factors. As an accessory analysis, we extracted/investigated patients with pain-relieving effects. However, no relationship existed between the pain-relieving effects of duloxetine and its plasma concentrations.

According to a review on the effects of duloxetine on fibromyalgia or painful diabetic neuropathy, pain was relieved through its direct actions on pain rather than depression improvement–related secondary effects. We previously selected milnacipran\textsuperscript{7} or duloxetine\textsuperscript{10} to treat BMS or AO and indicated the pain-relieving effects of these agents. In addition, we reported that these effects were similar regardless of the presence or absence of depressive symptoms at the start of the study. These findings are consistent with the results of the present study.

A study involving the administration of amitriptyline to patients with postherpetic neuralgia showed that its pain-relieving effects were more prominent when its plasma concentration was higher.\textsuperscript{22} Furthermore, a dose-titration study using imipramine for patients with DNP demonstrated that its pain-relieving effects were dose-dependent and also that these effects became more prominent with an increase in the plasma level of imipramine.\textsuperscript{23}
Another study investigated the efficacy of the serotonin-selective reuptake inhibitor (SSRI), paroxetine for DNP and indicated that its therapeutic effects were potentiated by an increase in its plasma concentration. A study on the SNRI, venlafaxine, involving patients with painful polyneuropathy reported that the mean plasma concentration of venlafaxine was higher in responders than in nonresponders, suggesting positive concentration effects. On the other hand, another study selected amitriptyline for patients with postherpetic neuralgia and indicated the therapeutic range of this drug. Furthermore, we previously examined the relationship between the effects of milnacipran on chronic nonorganic orofacial pain and its plasma concentration and reported that there was a significant quadratic regression, suggesting the presence of a therapeutic window reflecting a reduction in its effects at extremely high/low plasma concentrations.

On the other hand, a previous study on desipramine, amitriptyline, and fluoxetine involving patients with DNP showed that there was no relationship between their pain-relieving effects and dose or serum concentrations. A concentration-controlled trial on fluoxetine involving patients with chronic back pain found no relationship between its pain-relieving effects and plasma concentrations. The findings were similar to those of this study.

In the present study, there was no relationship between the pain-relieving effects of duloxetine and its plasma concentrations. This may be related to the properties of duloxetine as an SNRI. Venlafaxine, another SNRI, acts in a similar manner to SSRIs at a low dose, because its inhibitory effects on serotonin reuptake are more potent than those on noradrenaline reuptake. At a high dose, venlafaxine acts as an SNRI with sufficient inhibitory effects on noradrenaline reuptake. The pain-relieving effects of SNRIs are more prominent than those of SSRIs, and these pharmacological properties of venlafaxine may be involved in the previously mentioned positive concentration effects. The noradrenaline-serotonin transporter selectivity ratio of duloxetine is smaller than that of venlafaxine, and the former may act as an SNRI at a low dose/concentration. This may have contributed to the absence of positive concentration effects in this study, differing from venlafaxine. On the other hand, we previously reported that there was a therapeutic window between the plasma concentration of milnacipran and its pain-relieving effects, whereas no such relationship was observed in this study using duloxetine. The mechanism involved in this difference remains to be elucidated.

As another factor, there may have been placebo responders. The mechanism underlying placebo effects remains to be clarified; however, according to a study by Vase et al., the number of placebo responders has increased during the past 10 years based on the findings of randomized studies on neuropathic pain. On the other hand, placebo effects have not been controlled in most studies, making it difficult to demonstrate the efficacy of a new drug. The subjects in the present study may have included placebo responders, which may have made the concentration-response relationship unclear.

In the present study, 12 (15.6%) of the 77 participants dropped out because of adverse reactions. In our previous study on the effects of duloxetine on BMS and AO, patients dropping out because of adverse reactions accounted for 14.6%. This is consistent with the results of this study. Furthermore, in this study, dry mouth was noted in 4 patients (5.2%). A study involving the administration of the TCA amitriptyline to patients with chronic orofacial pain indicated that the incidence of dry mouth was 26.7%. In patients with oral diseases, adverse reactions in the oral cavity may prevent treatments. Because the affinity of duloxetine for muscarinic receptors is low, this drug may be more useful than TCAs for the treatment of diseases with oral symptoms, such as BMS and AO.

This study has limitations. The dose administered was restricted; the initial dose of duloxetine was established as 20 mg/d, and its dose after 2 weeks or later was increased to 40 mg/d. Because most subjects were middle-aged to elderly females, the dose was not increased to 60 mg/d, which is the maximum dose approved in Japan. Regarding the dose-plasma concentration relationship, only 2 doses, 20 and 40 mg/d, were adopted, and duloxetine at 40 mg/d was administered to most patients; therefore, comparisons were difficult. On the other hand, according to a study by Atkinson et al., the concentration–pain-relieving effect relationship in patients receiving drug therapy for neuropathic pain was clearer for drugs with linear pharmacokinetics. The concentration–pain-relieving effect relationship of duloxetine, which shows a linear dose-concentration relationship at 20, 30, and 40 mg, might be readily found. However, some studies examined the dose–pain-relieving effect relationship of duloxetine in fibromyalgia/DNP patients and reported that the effects were similar regardless of the dose administered. Although these studies investigated the relationship between pain-relieving effects and doses, but not plasma concentrations, these findings might support the results of the present study.

Other limitations are as follows: (1) The pain/depression assessment was conducted by physicians responsible for examinations/treatments because of an insufficiency of human resources. It is impossible to separately establish individuals responsible for the assessment and examinations/treatments using the current medical care system. (2) Patients of poor adherence were excluded based on extremely low plasma duloxetine concentrations; however, detailed medication adherence was not monitored by other methods. (3) This study had no placebo “run-in” period to identify and eliminate placebo responders.

**CONCLUSIONS**

With respect to the mechanism by which antidepressants relieve pain, serotonin and noradrenaline, increased by their reuptake-inhibiting actions, may potentiate endogenous pain control via the descending pain inhibitory system, thereby contributing to the appearance of effects. In the present study, there was no relationship between the pain-relieving effects of duloxetine and its plasma concentration. It may be difficult to explain the pain-relieving effects of duloxetine by only its plasma concentration, because pain occurs via a complex mechanism in which central and peripheral mechanisms are mixed. Various neurotransmitters, their receptors, ion channels, and inflammatory mediators may be involved in this mechanism. In the future, not only the pharmacokinetics of antidepressants, but also the kinetics of inflammatory cytokines, as other parameters involved in pain-relieving effects, need to be investigated in order to clarify the etiology/pathogenesis of chronic nonorganic pain in the orofacial region, as well as predictors of treatment responses.

**REFERENCES**


