Educational Case Report

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Duloxetine for the management of sensory and taste alterations, following iatrogenic damage of the lingual and chorda tympani nerve

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Abstract

Objectives: Nerve injury may lead to pain and sensory changes such as dysesthesia and paresthesia. Quantitative sensory testing (QST) is a psychophysical testing method used to quantify nerve damage and monitor its recovery. Duloxetine is used in the management of neuropathic pain conditions, but its effect on taste recovery has not been previously reported.

Case representation: A 65-year-old female, presented to the orofacial pain clinic, with a chief complaint of a burning sensation on the tongue, taste changes and a feeling of tightness beneath the tongue for five months. She reported that the complaints began subsequent to a complicated dental extraction during which she experienced trauma to the tongue. Patient was advised to take duloxetine 60 mg in divided doses three times daily. The assessment and monitoring of the recovery pattern were performed using QST. Electrical taste detection (mediated by chorda tympani) and electrical detection/tingling thresholds were performed at periodic intervals for up to a year following the nerve injury in the chorda tympani and lingual nerve territory. The patient reported complete recovery in taste sensation with duloxetine and this correlated with the QST results. QST documented at the end of one year revealed the electrical taste detection threshold and electrical detection threshold return to near normal values.

Conclusions: QST may be a useful diagnostic tool to assess and monitor lingual and chorda tympani nerve injuries. Duloxetine may aid in the recovery of the taste changes following lingual and chorda tympani nerve injury.

Keywords: duloxetine; nerve damage; quantitative sensory testing; sensation; taste; trauma.

Introduction

Nerve injury may lead to sensory changes, pain, numbness, allodynia (pain to a non-painful stimuli), paresthesia (an abnormal sensation) and dysesthesia (an unpleasant abnormal sensation) [1]. In many instances it may be iatrogenic. Quick and timely management are important to prevent further damage and restore altered sensory function.

Diagnosis of nerve injury often depends upon the history, clinical examination and diagnostic testing. QST is a psychophysical testing method used to assess, diagnose and monitor somatosensory deficits and sensory neuropathies [2]. It utilizes calibrated specific testing algorithms to objectively measure the response of subjects to graded noxious or innocuous stimuli such as thermal and mechanical stimuli. It has been validated in diabetic neuropathy, small fiber neuropathies and orofacial pain conditions such as temporomandibular disorders, oral malignancies, burning mouth syndrome and numb chin syndrome [2–5]. In the tongue, the electrical taste detection threshold is presumed to be dictated by the chorda tympani nerve (a branch of the facial nerve which supplies taste sensation to the anterior 2/3 of the tongue) and the electrical tingling sensation is thought to be mediated by the lingual nerve (a branch of the trigeminal nerve which supplies general sensation for the anterior 2/3 of the tongue) [6].
Once the patient is identified with nerve injury, appropriate measures may be taken depending upon the stage of nerve injury. In the early stages, the administration of anti-inflammatory drugs may be beneficial. If the damage persists longer, the treatment options may include medications such as tricyclic anti-depressants, anti-convulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and surgery or a combination [3].

The case report describes a patient with lingual and chorda tympani nerve injury approximately 5 months ago, secondary to surgical trauma during an extraction of the mandibular left third molar, and developed sensory and taste changes secondary to nerve damage. An initial assessment was made and the recovery pattern of sensory and taste function was monitored using QST. QST was performed at periodic intervals for up to one year following the nerve injury in the chorda tympani and lingual nerve territory. The changes in the sensory profile were correlated to the clinical symptoms. The patient reported complete recovery in taste sensation with duloxetine seven months following the treatment regimen and this correlated with QST results. QST documented at the end of one year after the injury revealed the electrical taste detection threshold and electrical detection threshold returned to near normal values (90% recovery). To our knowledge this is the first case report documenting recovery of taste and sensory function with duloxetine in cases of iatrogenic nerve injury.

Case report

A 65-year-old Caucasian female patient presented to the orofacial pain clinic with a chief complaint of a burning sensation on the tongue, loss of taste, and a feeling of tightness underneath the tongue for 5 months. The burning sensation extended from the tip of the tongue on the dorsal, ventral and lateral surfaces to the posterior surface of the tongue on the left side but did not cross the midline, consistent with the distribution of the lingual nerve. The patient visited a dentist five months previously for a routine oral prophylaxis and surgical extraction of the mandibular left third molar. During the course of the procedure, there was an accidental cut on the ventral surface of tongue, which started to bleed profusely. The dentist sutured it and stopped the bleeding. The patient reported that the sutures ruptured the same night and she visited the emergency department, where they were re-sutured. Immediately after re-suturing, she reported a burning sensation on the tongue, with a score of 6/10 on a visual analogue scale (VAS). The patient also reported tightness beneath the tongue accompanied with loss of taste, especially to sweet and salt tastes. The patient was advised that these symptoms would diminish over the next few days and was prescribed acetaminophen and ibuprofen. She was not aware of any diurnal variations in pain and could not associate the pain with any specific aggravating or alleviating factors. The patient's medical history was non-contributory. An extra oral clinical examination of the head and neck and cranial nerve screening did not reveal any significant abnormality. Temporomandibular joint and muscle examinations were performed per Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), and were negative for TMD [7]. The intraoral exam did not reveal any abnormalities in the teeth and soft tissues. A salivary gland assessment did not reveal any abnormality. An examination of the tongue did not reveal any motor pathology and there was no restriction in movement of the tongue. The tongue was normal in size, moist, with no coating on the dorsal surface or crenation on the lateral borders of the tongue. Fungiform papillae were within normal limits in appearance. The area of suturing had healed well and there was no visible scar at the time of examination. There was hyperalgesia to pinpricks in the distribution of the left lingual nerve. Full mouth radiographs and orthopantomograph (OPG) were negative for dental pathology. Routine blood serology tests, including complete blood counts, fasting, and postprandial blood sugar levels were within normal limits. Diagnostic application of a topical local anesthetic to the dorsal, ventral and lateral surface of the tongue resulted in partial alleviation of pain. Diagnostic testing included QST, which was performed in the chorda tympani and lingual nerve distribution. The patient was prescribed duloxetine 20 mg once daily. Over the course of two months, it was titrated to 60 mg in divided doses three times daily. She reported that her ability to taste started recovering 1 to 2 months after treatment but the burning sensation on the tongue persisted. Eventually, 7 months after treatment, she reported complete recovery of the taste and burning sensation.

Diagnostic testing

QST was performed to assess the extent of damage and functioning of the lingual and chorda tympani nerve. The Neurometer current perception threshold (CPT) test (Neurometer, NS300, Neurotron Inc. Denver, Colorado, USA) was used to monitor the progress of the sensory nerve function in the chorda tympani and lingual nerve.
distribution. The patient was tested four times over a period of one year after the initial nerve injury using the CPT tests in the chorda tympani and lingual nerve distribution of the affected and unaffected site.

An electrical taste detection threshold and an electrical/tingling threshold testing were performed using the ascending method of limits. The stimulating current was increased in intensity gradually by the operator until the patient indicated they could detect a metallic taste or a tingling sensation [6]. The Neurometer CPT electrode delivered an electric current through two gold plated electrodes placed on the dorsal surface of the tongue or the mental nerve territory using three different frequencies of electric currents of 5, 250, and 2000 Hz. Each frequency checks specific functionality of a sensory nerve fiber. The 5 Hz frequency tests C fibers, 250 Hz frequency tests A-delta fibers while A-beta fibers were tested by the 2,000 Hz frequency. Each site underwent three tests for detection thresholds and the mean value was calculated. The reference value for face, finger and toe has been previously established and can be used for comparison (Neuval® Database II – Normative Data, Neurotron, Inc. Baltimore, MD, USA, 2001, https://www.neurotron.com/ Normative_Current_Perception_Threshold_CPT_Values. html, accessed 24 Feb 2020). In addition, in otherwise healthy individuals with nerve injury or trauma, the affected site can be compared with the normal/contralateral side in the same subject.

CPT values for the chorda tympani and lingual nerve

The electrodes were placed on the dorsolateral surface of the tongue on the ipsilateral and contralateral sides. The tests were carried out in a quiet room with ambient temperature settings. The tests were explained to the patient and a trial was done before commencing the actual tests. The same operator conducted all the tests. The patient was informed that while the test was in progress, she had control of the testing machine. When she felt a metallic taste [6] or electrical/tingling sensation, she could stop the test by pressing on the control button. Neurometer CPT runs tests randomly with the three frequencies mentioned above (5, 250, and 2,000 Hz) for profiling C, A-delta and A-beta fibers, respectively. In each visit, the testing was performed three times for each site and the mean was calculated. The patient underwent testing four times during her follow up, and three more times up until one year following the nerve injury.

Results

Chorda tympani: On the first visit, the patient complained of loss of taste, which is represented by of the ipsilateral side of the chorda tympani nerve. During the follow up visits subsequent to treatment with duloxetine, taste improved. This was reflected in the CPT values for the chorda tympani, which approached the values for the unaffected contralateral side. In the last visit, the patient reported no taste alterations and was reflected in the CPT values (Table 1).

Lingual nerve: On the first visit, the patient complained of a burning sensation on the left side of tongue along with the tightness underneath the tongue. This burning sensation was represented by of the ipsilateral side of the lingual nerve in CPT values. During the follow up visits, the pain decreased however there was an increase in tightness deep underneath the tongue. At the second visit after treatment with duloxetine, the patient reported that the burning sensation had changed to pain and converged on the tip of tongue. The tightness underneath the tongue was completely eliminated. At the last visit, the comparison of CPT values between the ipsilateral side and the contralateral side showed almost normal values and this was consistent with the patients report of reduction of pain on the tip of the tongue (Table 2).

Based on the history (history of an iatrogenic nerve injury, burning and constant pain, taste changes and no known aggravating and relieving factors), clinical examination (hyperalgesia on the dorsum of the tongue on the left side, neurosensory mapping, a clinical exam negative for dental issues and intraoral pathology including the tongue and salivary gland and partial alleviation of pain

| Frequency | Right (control) | Left |
|-----------|----------------|------|
| 5 Hz      | 5–15 (Baseline) | 5–15 (Baseline) |
|           | 5–15 (First visit) | 5–15 (First visit) |
|           | 5–15 (Second visit) | 5–15 (Second visit) |
|           | 5–15 (Third visit) | 5–15 (Third visit) |
| 250 Hz    | 25–35 (Baseline) | 25–35 (Baseline) |
|           | 25–35 (First visit) | 25–35 (First visit) |
|           | 40–50 (Second visit) | 40–50 (Second visit) |
|           | 35–45 (Third visit) | 35–45 (Third visit) |
| 2,000 Hz  | 75–85 (Baseline) | 95–105 (First visit) |
|           | 95–105 (First visit) | 115–125 (Second visit) |
|           | 115–125 (Second visit) | 125–135 (Third visit) |
|           | 125–135 (Third visit) | 125–135 (Third visit) |
Table 2: Quantitative sensory testing threshold testing of lingual nerve distribution First, Second, and Third visit (Baseline done prior to initiation of duloxetine therapy).

| Frequency | Right (control) | Left |
|-----------|-----------------|------|
| 5 Hz      | 5–15 (Baseline) | 5–15 (Baseline) |
| 5 Hz      | 5–15 (First visit) | 5–15 (First visit) |
| 5 Hz      | 5–15 (Second visit) | 5–15 (Second visit) |
| 15–25     | 15–25 (Third visit) | 15–25 (Third visit) |
| 250 Hz    | 70–80 (Baseline) | 25–35 (Baseline) |
| 250 Hz    | 85–95 (First visit) | 40–50 (First visit) |
| 250 Hz    | 70–80 (Second visit) | 45–55 (Second visit) |
| 250 Hz    | 70–80 (Third visit) | 60–70 (Third visit) |
| 2,000 Hz  | 115–125 (Baseline) | 85–95 (Baseline) |
| 2,000 Hz  | 105–115 (First visit) | 95–100 (First visit) |
| 2,000 Hz  | 125–135 (Second visit) | 115–125 (Second visit) |
| 2,000 Hz  | 125–135 (Third visit) | 105–115 (Third visit) |

QST may aid in the diagnosis and assessment of the extent and magnitude of the disease, determine prognosis, dictate the treatment plan and influence the treatment outcome [2]. It can also help in mapping the somatosensory dysfunction area and in particular can lead clinicians to obtain qualitative (e.g., allodynia, dysesthesia or paresthesia) as well as quantitative (hyperesthesia and hyposthesia) information about the sensory dysfunction [2, 13]. Neurometer CPT, used to assess electric taste detection threshold, has been previously validated. It can be done in clinical settings and along with taking a proper patient history and clinical examination can aid in the assessment, diagnosis and monitoring of the effects of treatment. Electrical stimulation tests of the chorda tympani and lingual nerve have the advantage of bypassing receptors (and conditions affecting the receptors such as receptor fatigue, suppression or sensitization) and stimulating the primary afferent axons directly [6].

Following nerve injury, partial recovery of sensation occurs within a period of 6 month post injury. However, a universal consensus on early vs. late nerve repair is still controversial. Studies indicate that early repair has a higher success as compared to late repair [14, 15].

In cases of lingual nerve and chorda tympani nerve injury, patients may present with varying degrees of taste alterations and burning sensation depending on the extent of the nerve injury. Studies indicate that in instances of damage to chorda tympani, there is recovery of somatosensory function first as compared to taste [16]. Chronic nerve injury associated with taste changes have been attributed to changes in peripheral processing, changes in sodium transduction pathway [17], central processing and microglial responses [18]. In the present case the patient initially presented 5 month’s post nerve injury, but started recovering the taste alteration followed by diminished burning sensation after duloxetine was taken for 2 months. We postulate that in this case duloxetine may have been an adjunctive aid to facilitate early recovery of taste in addition to the recovery of sensation.

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) and acts by blocking the reuptake of serotonin and norepinephrine. It is used to treat small fiber neuropathies, chronic pain, fibromyalgia, and depression [19], but its effect on taste recovery has not been previously documented to our knowledge. Although the major effect of duloxetine is through serotonin norepinephrine reuptake inhibition, recent studies have suggested that it may have an inhibitory effect on persistent late sodium channels [20] and inhibitory effects on microglia [21, 22].

Studies show that duloxetine can reduce mechanical allodynia in an animal model of inflammatory pain [23] and
can induce anti-inflammatory effects by lowering TNF-α levels aiding in sensory and the regenerative process of the nerve [24]. Animal studies show duloxetine can display neuroprotective effects by preventing hippocampal neuronal death [25]. These peripheral and central mechanisms may possibly act in concert with serotonin norepinephrine reuptake inhibitory effect and result in recovery of taste and burning sensation following possible lingual and chorda tympani nerve injury.

Taste changes are often reported as idiopathic, however there can be many reasons for chemosensory defects including surgical trauma, head injury, hypothyroidism, ear surgery, third molar extractions, neurotoxicity to local anesthetics, radiation therapy, intubation, and direct nerve injuries [26–28]. Dental procedures and gustatory disorders have frequently been reported previously, but the evidence is poor on the correlation. Many of the reported studies are case studies and the underlying mechanisms are poorly understood. In the present case, duloxetine may have facilitated the recovery of partial nerve damage helping in retrieving of sensation and taste. The role of duloxetine in recovery of taste has not been previously reported and further research is needed to uncover the mechanisms by which it facilitates this recovery.

Studies have shown that QST can assist determine if the nerve injury has an inflammatory origin as opposed to permanent nerve damage. Neuropathic pain of inflammatory origin may present with a decrease in the detection threshold of the affected nerve and is more likely to be reversible. The condition is more likely to recover when anti-inflammatory medications are administered in the early stages. In instances of permanent nerve damage an elevated detection threshold may be observed. The nerve damage in these instances is more severe and likely to be permanent depending on the degree of nerve injury and may require neuropathic pain pharmacotherapy [29]. QST used in the evaluation of painful neuropathies, only may express whether there is a degeneration of nerve fibers, but not explain the pain itself, which is often due to hyper excitability of nerve fibers. In the present case QST aided in the analysis of nerve damage and recovery and we postulate that the recovery was facilitated by duloxetine. Future studies are needed to uncover mechanisms by which duloxetine facilitates this recovery and works exclusively on different nerve fibers.

In our patient we used duloxetine to treat chronic iatrogenic nerve injury and objectively assessed and monitored the effect of treatment using electrical taste and tingling detection thresholds. The perceptual recovery of taste correlated with sensory changes in the chorda tympani, returning to almost normal values at seven months following treatment. The recovery of the lingual nerve function was also aided by duloxetine, and resulted in the reduction of the burning sensation.

In the clinic it is important to first diagnose the basic etiology of the pain and then employ the treatment and management accordingly. In the scenario of this particular case, we were able to follow up with the area of the sensory changes in the lingual and chorda tympani nerve after the iatrogenic injury to the lingual nerve with QST. The patient was prescribed duloxetine 60 mg in divided doses daily to aid in the recovery of the nerve injury. The treatment regimen also aided in the complete recovery of taste sensation, which correlated with the sensory recovery pattern documented using QST. On this basis, the patient was also suggested not to undergo any further interventional treatments.

QST may be an asset to pain physicians, especially those who deal with patients with posttraumatic neuropathies. QST may aid in diagnosis, mapping the somatosensory area and determining the prognosis and management.

**Conclusion**

QST may be a useful diagnostic tool to assess and monitor lingual nerve injuries. Duloxetine may aid in the recovery of the taste changes following lingual nerve neuritis.

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**References**

1. Harold Merskey NB. Task force on taxonomy of the international association for the study of pain. Classification of chronic pain, 2nd ed. In: N.B. Harold Merskey, editor. Seattle: IASP Press; 1994.
2. Backonja MM, Attal N, Baron R, Bouhassira D, Drangholt M, Dyck PJ, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. Pain 2013;154:1807–19.
3. Eliav E, Gracely RH, Nahlieli O, Benoliel R. Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain 2004;18:339–44.
4. Yang G, Su S, Jie H, Baad-Hansen L, Wang K, Yan S, et al. Somatosensory profiling of patients with burning mouth syndrome and correlations with psychologic factors. J Oral Facial Pain Headache 2019;33:278–86.
5. Kalladka M, Proter N, Benoliel R, Czerninski R, Eliav E. Mental nerve neuropathy: patient characteristics and neurosensory changes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:364–70.

6. Eliav E, Kamran B, Schaham R, Czerninski R, Gracey RH, Benoliel R. Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. J Am Dent Assoc 2007;138:628–33.

7. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the international RDC/TMD consortium network* and orofacial pain special interest group. J Oral Facial Pain Headache 2014;28:6–27.

8. Rolke R, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150:439–50.

9. Hansson P, Backonja M, Bouhassira D. Usefulness and therapeutic implications of quantitative sensory testing of neuropathic pain patients: potential mechanistic and therapeutic implications. Curr Pain Headache Rep 2012;16:199–206.

10. Pfau DB, Geber C, Birklein F, Treede RD. Quantitative sensory testing of neuropathic pain patients: potential mechanistic and therapeutic implications. Curr Pain Headache Rep 2012;16:199–206.

11. Backonja MM, Walk D. QST in peripheral nerve injury pain disorders. Pain 2012;153:736–7.

12. Smith KG, Robinson PP. An experimental study on the recovery of the lingual nerve after injury with or without repair. Int J Oral Maxillofac Surg 1995;24:372–9.

13. Magda P, Latov N, Renard MV, Sander HW. Quantitative sensory testing: high sensitivity in small fiber neuropathy with normal NCS/EMG. J Peripher Nerv Syst 2002;7:225–8.

14. Håkansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain 2007;129:256–9.

15. Smith KG, Robinson PP. An experimental study on the recovery of the lingual nerve after injury with or without repair. Int J Oral Maxillofac Surg 1995;24:372–9.

16. Eckardt A, Meier K, Hausamen JE. Histomorphometric results after late microsurgical nerve grafting of the inferior alveolar nerve of the rabbit. Int J Oral Maxillofac Surg 1999;19:312–4.

17. Maeda E, Katsura H, Nin T, Sakaguchi-Fukunaga A, Mishiro Y, Sakagami M. Change of somatosensory function of the tongue caused by chorda tympani nerve disorder after stapes surgery. Laryngoscope 2018;128:701–6.