

Changes in Corrected QT Interval May Be Associated with Clinical Responses in Burning Mouth Syndrome

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ABSTRACT

Backgrounds: Burning mouth syndrome (BMS) is characterized by a burning sensation of the oral mucosa in the absence of underlying dental causes. Only a minority of BMS patients will achieve satisfactory pain relief and little is known about clinical makers for the response. The objective of this study was to consider whether corrected QT interval (QTc) is a useful biomarker for clinical responses.

Methods: We conducted a single-center retrospective observational study and evaluated 51 BMS patients treated with amitriptyline. We calculated QTc changes with amitriptyline and examined the relationship between changes in QTc and visual analogue scale (VAS).

Results: Of 51 subjects, 13 (25.5%) were amitriptyline-responders and 38 (74.5%) were non-responders. The changes in QTc interval were significantly correlated with changes in VAS (Spearman's rank correlation coefficient $r = 0.389$, $p = 0.006$).

Conclusions: Changes in QTc interval may be a non-invasive estimation of clinical responses in BMS patients.

KEY WORDS

amitriptyline, autonomic nervous function, burning mouth syndrome, QTc interval

INTRODUCTION

Burning mouth syndrome (BMS) is characterized by a burning sensation of the oral mucosa in the absence of underlying medical or dental causes, mainly found in middle aged or elderly women¹⁾. BMS patients are often transferred to a psychiatric hospital because of no underlying physical abnormalities. Amitriptyline, a tricyclic antidepressant, has been a first-line treatment for BMS as it helps inhibit pain signals by activating descending pain inhibitory pathways²⁾. However, only a minority of people will achieve satisfactory pain relief and little is known about clinical makers for the response to amitriptyline. We previously reported that changes in non-stimulated salivary flow by amitriptyline were involved in clinical responses of BMS patients, which indicated changes in sympathetic and parasympathetic tones³⁾. Autonomic nervous function has an influence on corrected QT interval (QTc) and may be related to pain control in patients with chronic oral pain such as BMS and atypical odontalgia⁴⁾. The objective of this study was to investigate the relationship between QTc changes and the response to amitriptyline in BMS patients.

SUBJECTS AND METHODS

We conducted a single-center retrospective observational study and evaluated 51 BMS patients treated with amitriptyline from January 2016 to December 2017. Participants received 12-lead electrocardiography examination and visual analogue scale (VAS) at baseline and a month. Exclusion criteria included hypokalemia and any cardiac diseases, which have a potential of QTc prolongation. We calculated QTc interval by the Bazett formula. Amitriptyline-responders were defined as a decrease in VAS by more than 20 mm. We compared QTc changes with amitriptyline between responders and non-responders and examined the relationship between changes in VAS and QTc interval. The statistical analysis was performed by Mann-Whitney U test and Spearman's rank correlation. The ethics committee of Tokyo Medical and Dental University and Sunlight Brain Research Center approved this study and informed consent was obtained in the form of opt-out on the in-hospital bulletin board.

RESULTS

Of 51 subjects, 13 (25.5%) were responders and 38 (74.5%) were non-responders. The changes in QTc of responders were significantly

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Table 1. Clinical characteristics of subjects: Age, female ratio, amitriptyline dosage, improvement in VAS, baseline heart rate, baseline QTc, changes in heart rate, and changes in QTc.

	Responder	Non-responder	p-value
Sample size	13	38	/
Age, years, mean \pm SE	63.1 \pm 3.9	60.7 \pm 1.8	0.3357
Female ratio, %	76.9	78.9	0.8783 ^b
Amitriptyline dosage, mg/day	17.5 \pm 1.6	16.7 \pm 0.9	0.7375
Improvement in VAS, mm	34.8 \pm 3.0	-5.0 \pm 3.7	0.000*
Baseline heart rate, beats/min	62.4 \pm 2.2	65.4 \pm 2.2	0.6734
Baseline QTc, msec	412.2 \pm 7.7	419.7 \pm 3.9	0.4689
Change in heart rate, beats/min	9.2 \pm 2.4	6.3 \pm 1.3	0.2054
Change in QTc, msec	4.2 \pm 4.8	-9.4 \pm 2.7	0.011*

Abbreviation: VAS, visual analogue scale; QTc, corrected QT interval.
Mann-Whitney U test, * p<0.05, ^bChi-squared test

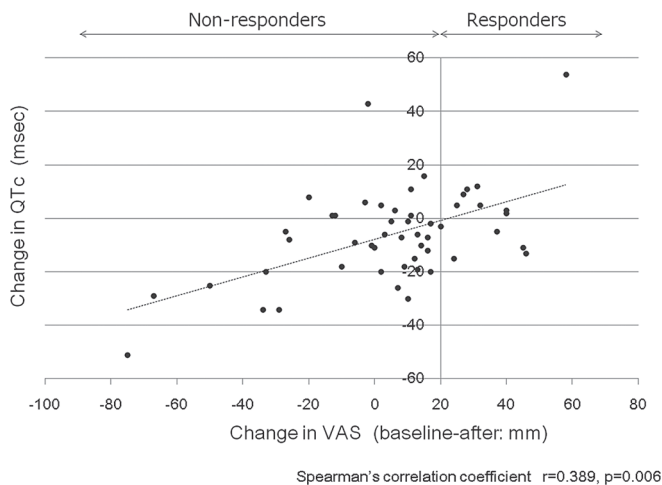


Figure 1. The relationship between changes in QTc and VAS

longer than those of non-responders, although there were no differences in age, female ratio, amitriptyline dosages, and baseline QTc levels. Responders revealed a small increase in QTc (4.2 msec), whereas non-responders indicated a small decrease in QTc (-9.4 msec) (Table 1). The changes in QTc interval were significantly correlated with changes in VAS (Spearman's rank correlation coefficient $r = 0.389$, $p = 0.006$; Figure 1).

DISCUSSION

The QTc interval is influenced by autonomic nervous function and various drugs that affect human Ether-a-go-go Related Gene (hERG)⁹. Amitriptyline is known to have a risk of QTc prolongation⁶. However, analgesic dose of amitriptyline (below 30 mg) does not prolong QTc interval because low dose amitriptyline is unlikely to block hERG^{4,7}. The changes in QTc in this study may be involved in autonomic nervous function. The sympathetic nerves shorten QTc and parasympathetic nerves prolong it⁸). Persistent pain induces brainstem noradrenergic

sympathetic activation that enhances descending pain facilitation from dorsal reticular nucleus⁹). Sympathetic overactivity is associated with chronic pain intensity, while parasympathetic nerve stimulation efficiently modulates nociception¹⁰). The QTc shortening in non-responders indicated an increase in sympathetic tone and pain facilitation from brainstem, whereas a slight QTc increase in responders revealed an increase in parasympathetic tone and pain relief.

In conclusion, changes in QTc interval may be a non-invasive estimation of clinical responses in BMS patients. Additional high-quality studies are needed to elucidate the relationship between QTc interval and autonomic nervous function and to establish appropriate indicators for clinical responses in BMS patients.

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