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The QTc shortening with amitriptyline may indicate treatment resistance in chronic nonorganic orofacial pain

Takeshi Watanabe, DDS, PhD[1], Kaoru Kawasaki, DDS[1], Trang T.H Tu, DDS[1], Takayuki Suga, DDS[1], Shiori Sugawara, DDS[1], Lou Mikuzuki, DDS[1], Anna Miura, DDS[1], Yukiko Shinohara, DDS[1], Tatsuya Yoshikawa, DDS[1], Miho Takenoshita, DDS, PhD[1], Akira Toyofuku, DDS, PhD[1], Takahiko Nagamine, MD, PhD[2]

[1]*Department of Psychosomatic Dentistry, Tokyo Medical and Dental University Graduate School of Medical and Dental Science*
[2]*Sunlight Brain Research Center*

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To the Editor: Chronic nonorganic orofacial pain (CNOP), such as burning mouth syndrome and atypical odontalgia, is characterized by debilitating intraoral burning sensation for which no localized or systemic cause can be found [1]. The effective management of CNOP remains a therapeutic challenge. Amitriptyline is widely used as an analgesic in chronic pain as it helps inhibit pain signals by activating descending pain inhibitory pathways. However, amitriptyline is known to prolong QTc interval in a dose dependent manner, which may be associated with an increased risk of ventricular arrhythmias. Little is known about the QTc lengthening effect of amitriptyline at analgesic dosages (10-30 mg/day). The objective of this study was to evaluate QTc changes in CNOP patients treated with amitriptyline.

Here, we investigate changes in QTc by amitriptyline treatment, based on a month prospective-designed method in Japanese middle-aged CNOP patients. Patients with a diagnosis of burning mouth syndrome or atypical odontalgia from April 2016 to March 2017 at Tokyo Medical and Dental University were eligible to enter this study. The exclusion criteria were as follows; (1) undergoing treatment of analgesics, selective serotonin reuptake inhibitors (SSRIs), or serotonin and norepinephrine reuptake inhibitors (SNRIs), (2) taking any medicine that influence QTc interval, and (3) medical conditions such as hypokalemia and cardiac diseases which were supposed to prolong QTc interval. Participants received 12-lead electrocardiography (ECG) examination and visual analogue scale (VAS) at baseline and a month. We calculated QTc interval by the Bazett formula. The ethics committee of Faculty of Dentistry Tokyo Medical and Dental University approved this study, and informed consent was obtained from all subjects. The study population consisted of 9 male (including 5 burning mouth syndrome and 4 atypical odontalgia) with a mean age of 57.2 years, and 23 female (including 16 burning mouth syndrome and 7 atypical odontalgia) with a mean age of 54.6 years. Amitriptyline dose was 18.2 ± 1.2 mg/day (mean ± SE). Amitriptyline improved VAS scores from 50.7 ± 5.1 to 45.9 ± 4.6 (paired t test, $p<0.05$), and did not prolong QTc interval statistically (baseline QTc, 413.3 ± 3.7 msec; QTc after a month, 408.4 ± 3.2 msec). However, a decrease in QTc was significantly associated with

Address for correspondence; Takahiko Nagamine, MD, PhD, Sunlight Brain Research Center, 4-13-18 Jiyugaoka, Hofu, Yamaguchi 747-0066, Japan. Tel: +835-25-6610 e-mail: tnagamine@outlook.com

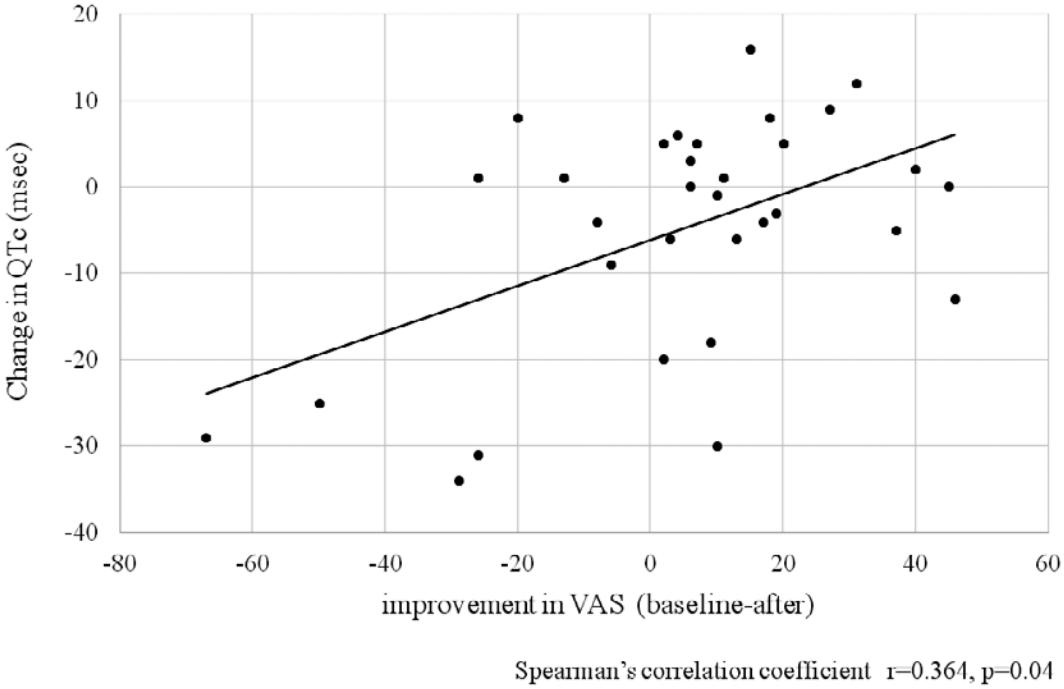

Figure 1. Relationship between changes in QTc interval and clinical outcomes

an increase in VAS score (Spearman's correlation coefficient r=0.364, p=0.04; Figure 1).

The important findings of our study are that low dose of amitriptyline (<30 mg/day) has proved to be safe and effective for CNOP and a decrease in QTc with amitriptyline indicated treatment resistance. The QTc intervals are influenced by myocardial damages, potassium concentration, various drugs that affect the human Ether-a-go-go Related Gene (hERG) channel, and autonomic nervous function [2]. Since it's unlikely that low dose amitriptyline clinically blocks hERG channel [3] and myocardial diseases and hypokalemia were excluded in this study, the change in QTc may indicate alteration in autonomic nervous function. The sympathetic nerve functions shorten QTc intervals, while the parasympathetic nerve functions prolong them. Recent work strongly suggests that cardiovascular sympathetic overactivity increases chronic pain intensity, while parasympathetic nerve stimulation efficiently modulates nociception and pain processing [4]. Chronic pain sometimes induces brainstem noradrenergic sympathetic activation that enhances descending pain facilitation from the dorsal reticular nucleus [5]. In amitriptyline-resistant CNOP patients, amitriptyline-induced noradrenaline increase may enhance pain facilitation from the brainstem, counteracting their analgesic effects of descending pain inhibitory pathway. Thus, a decrease in QTc with amitriptyline may indicate noradrenaline related sympathetic overactivity, resulted in pain intensity in amitriptyline-resistant CNOP patients. The changes in QTc may be a non-invasive estimation of clinical response to amitriptyline in CNOP patients.

The limitations of this study include a small sample size and lack of control group. Moreover, the association between changes in QTc and improvement in VAS may be coincidental. Due to these limitations, any conclusions must be considered preliminary and in need of replication.

Disclosure Statement

The authors have no conflicts of interest relevant to the content of the article.

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