Electrocardiogram Characteristics of Methadone and Buprenorphine Maintained Subjects

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Online Publication Date: 12 June 2008

To cite this Article Athanasos, Peter, Farquharson, Aaron L., Compton, Peggy, Psaltis, Peter and Hay, Justin(2008)'Electrocardiogram Characteristics of Methadone and Buprenorphine Maintained Subjects'.Journal of Addictive Diseases,27:3,31 — 35

To link to this Article: DOI: 10.1080/10550880802122596

URL: http://dx.doi.org/10.1080/10550880802122596
Electrocardiogram Characteristics of Methadone and Buprenorphine Maintained Subjects

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ABSTRACT. There has been recent concern about the association between high dose methadone and prolongation of QTc in the electrocardiogram. QTc is the time from the beginning of the QRS complex to the end of the T wave as measured on an electrocardiogram and corrected for heart rate. To date, no association has been made between methadone and buprenorphine in commonly used doses and prolonged QTc. Electrocardiograms were performed on groups of methadone (n = 35, mean daily dose ± standard deviation, 69 ± 29 mg) and buprenorphine (n = 19, mean daily dose 11 ± 5 mg) subjects and a group of non-opioid dependent controls (n = 17). Mean QTc did not differ (p = 0.45) between methadone, buprenorphine, or controls. Methadone subjects were significantly (odds ratio of 7.8) more likely to have U waves than buprenorphine and controls combined. Methadone subjects with U waves were maintained on higher (p = 0.004) doses (89 ± 29 mg/day) than methadone subjects without U waves (60 ± 24 mg/day). Methadone subjects taking 60 mg and above had higher (p = 0.02) QTc (405 ± 29 milliseconds) than methadone subjects taking less than 60 mg per day (381 ± 27 milliseconds). Although an association is thought to exist between high methadone doses and elongated QTc, methadone and buprenorphine, at commonly used daily doses, remain safe agents for opioid substitution therapy.

KEYWORDS. Methadone, electrocardiogram, elongated QTc, buprenorphine

INTRODUCTION

Opioid replacement therapy has been used to treat heroin addiction for more than 40 years,1 and commonly used agents are the agonist methadone and mixed agonist/antagonist buprenorphine. The long duration of action and the safety profiles of these medications have made them popular agents to treat not only opioid addiction, but also chronic pain.2,3 However,
there has been recent concern about the prolongation effects of high doses of methadone and methadone induction on the corrected QT interval (QTc). The QTc is the time from the beginning of the QRS complex to the end of the T wave as measured on an electrocardiogram (QT) and corrected for heart rate (QTc). The QRS complex represents ventricular depolarization and the T wave represents ventricular repolarization. Prolonged QTc intervals have been associated with the often fatal torsades de pointes.

All wave forms in the electrocardiogram can be classified as depolarizations or repolarizations. The QRS complex represents ventricular depolarization. Ventricular repolarization is represented by the T wave and the U wave. Although the physiological U wave (less than one-fourth the size of the T wave) may be observed in normal adults, it is particularly prevalent in patients with congenital long QT syndrome and may therefore be indicative of this condition.

This study examined the effects of commonly used buprenorphine and methadone maintenance doses on the QTc and prevalence of U waves in a dose-dependent fashion. The subjects were then compared to a group of weight and age matched non-opioid dependent control subjects.

**METHODS**

The Research Ethics Committee of the Royal Adelaide Hospital in Adelaide, Australia and the Institutional Review Board, Friends Research Institute in Los Angeles, California, approved the medical assessment of subjects and measurement of the electrocardiograms. Utilizing a survey design, the study was conducted in 3 groups of subjects: methadone maintained subjects (methadone subjects), buprenorphine maintained subjects (buprenorphine subjects), and healthy, non-opioid dependent control subjects (control subjects). All subjects provided written informed consent. Methadone and buprenorphine subjects had been receiving their maintenance opioid dose once daily for the treatment of opioid dependency for a minimum of 1 month with no dose changes.

A medical history, physical examination, and standard 12-lead electrocardiogram were used to assess for the following exclusion criteria: pregnancy or lactation, consumption of any medications that delayed cardiac depolarization or affected methadone and buprenorphine metabolism, infection with the human immunodeficiency virus (HIV), liver enzyme [ALT (alanine aminotransferase) or AST (aspartate aminotransferase)] values more than 3 times normal range, and any history of structural heart disease, hypertension, supraventricular rhythms, or atrial fibrillation. Subjects were asked not to use any analgesics or illicit substances for 24 hours prior to electrocardiogram measurement. Opioid dependent and control subjects were excluded from the study if they presented to two experienced clinicians showing any signs of intoxication from any substance.

**Subjects**

Thirty-five methadone maintained subjects (23 men and 12 women) with a mean ± standard deviation (SD) age of 35 ± 8 years (range: 24 to 48 years) and weighing 73 ± 14 kg (range: 43 to 101 kg) who had been in methadone maintenance treatment for a duration of treatment for 66 ± 86 weeks (range: 4 to 312 weeks) for 15 ± 15 weeks (range: 4 to 60 weeks) with no dose change were recruited.

Nineteen buprenorphine maintained subjects (11 men and 8 women) with a mean ± SD age of 34 ± 6 years (range: 24 to 42 years) and weighing 69 ± 13 kg (range: 49 to 97 kg) who had been in buprenorphine maintenance treatment for a duration of treatment for 40 ± 26 weeks (range: 8 to 96 weeks) for 18 ± 14 weeks (range 4 to 52 weeks) with no dose change were recruited.

Seventeen control subjects (9 men and 8 women) with a mean ± SD age of 31 ± 8 years (range: 20 to 41 years) and weighing 78 ± 17 kg (range: 54 to 102 kg) were also recruited.

**Procedures and Definitions**

All electrocardiograms were performed between 9 a.m. and 3 p.m. using the same model machine and recorded at 25 mm/second paper speed with standard conventional amplification (1 mV = 10 mm). After they were recorded, electrocardiograms were blinded and randomized.
They were then analyzed manually by a single, independent cardiologist. Electrocardiogram intervals were defined by standard criteria. All QT intervals were corrected using Bazett’s formula: $QTc = \frac{QT \text{ interval (in milliseconds)}}{\text{the square root of the preceding RR interval (in seconds)}}$. The QTc interval is normally less than 450 ms in women and less than 430 ms in men. QT intervals were measured in the limb lead that best showed the end of the T wave. U waves were included in the QT interval analysis (e.g., QTU wave only if they merged with the T wave). All U waves were classified as physiological (less than one-fourth T wave size). All subjects were in either sinus rhythm or sinus bradycardia.

**Analysis**

Data are presented as mean ± SD (with 95% confidence intervals [95% CI]). One-way analysis of variance was used to compare QTc intervals between groups (methadone, buprenorphine, and control subjects). Unrelated samples t-tests were used to compare differences in subjects taking 60 mg/day and above and those taking less than 60 mg/day of methadone and to compare methadone subjects with and without U waves. Chi square was used to compare differences in the presence of U waves between methadone, buprenorphine, and control subjects. Fisher’s exact ratio was used to calculate odds ratio in the frequency of U waves between methadone subjects and the combined buprenorphine and control subjects.

**RESULTS**

Mean QTc intervals did not differ ($p = 0.27$) between the methadone (407 ± 23 milliseconds; range: 343 to 438 milliseconds), buprenorphine (407 ± 18 milliseconds; range: 377 to 441 milliseconds) or control (397 ± 21 milliseconds; range: 369 to 446 milliseconds) groups. There was no correlation between methadone dose and QTc interval ($p = 0.25$). However, methadone subjects on daily methadone doses of 60 mg/day and above had higher QTc intervals ($p = 0.02$; 95% CI = 4.0 to 45; 405 ± 29 milliseconds; range: 350 to 460 milliseconds) than methadone subjects on less than 60 mg/day (381 ± 27 milliseconds; range: 330 to 440 milliseconds) (Figure 1). Two male methadone subjects (431 and 458 milliseconds) and one male control subject (430 milliseconds) had prolonged QTc intervals. There was a significant difference ($p = 0.012$) in the frequency of U waves between methadone, buprenorphine, and control subjects. Methadone subjects were significantly more likely (11 of 24; 46%) (odds ratio of 7.8) to have U waves present then buprenorphine (0/19; 0%) and control subjects (2/15; 13%) combined. Methadone subjects with U waves were maintained on significantly higher ($p = 0.004$; 95% CI = 10.5 to 49; 89 ± 29 mg/day; range: 35 to 145 mg/day) daily doses of methadone than methadone subjects without U waves (60 ± 24 mg/day; range: 15 to 115 mg/day) (Figure 2).

**DISCUSSION**

In this study, the group of methadone subjects maintained 60 mg/day and above were found to have significantly longer QTc intervals than those who maintained between 15 and 60 mg/day (although still within normal QTc ranges). Methadone subjects were approximately 8 times more likely to have U waves than the control and buprenorphine subjects combined, and methadone subjects with U waves...
waves were maintained on significantly higher doses of methadone than methadone subjects without U waves.

The withdrawal of the maintenance opioid L-\(\alpha\)-acetyl-methadol hydrochloride (LAAM) from the European market in 2001 following two reported cases of torsade de pointes and one sudden, likely related death has led to a general concern about the cardiac safety of maintenance opioids for the treatment of opioid dependency.\(^{10}\)

More recently, several studies have suggested that electrocardiogram changes due to the use of heroin, methadone, and other drugs of abuse may contribute to the often fatal torsade de pointe in opioid dependent patients.\(^{11-13}\)

Lipski et al.\(^{14}\) were among the first to examine the electrocardiograms of heroin users, methadone subjects (who occasionally used illicit drugs), and a drug-free control group. They found that unlike control subjects (0%), heroin users (19%), and methadone subjects (34%) had prolonged QTc intervals. The results from this study suggest that commonly used maintenance doses of methadone and buprenorphine do not result in abnormally long QTc intervals. However, there is evidence for a dose dependent effect. Higher doses of methadone (60 to 100 mg/day) are more effective in promoting illicit opioid abstinence than lower doses (20 mg/day).\(^{15}\)

We found that subjects on higher doses of methadone (60 to 145 mg/day) were found to have significantly longer QTc intervals than those maintained on lower doses (15 to 60 mg/day). Unlike methadone, buprenorphine does not have an effect on the QTc interval at commonly used dose ranges.

U waves have been associated with a variety of conditions, including drug-induced or congenital long-QT syndromes. There are two major classifications for the U wave, the pathophysiological (larger than the T wave) and the physiological (less than one-fourth the T wave size). All U waves detected in this study were classified as physiological. As stated, the physiological U wave is particularly prevalent in patients with the congenital long QT syndrome.\(^{6}\)

Lipski et al.\(^{14}\) found that 32% of methadone maintained patients had pathophysiologial U waves. We found that 46% of methadone subjects had physiological U waves, and they were approximately 8 times more likely to have physiological U waves than buprenorphine and control subjects combined. As with the QTc intervals, the manifestation of U waves was also dose-dependent in the sample; methadone subjects with U waves were maintained on nearly 90 mg/day of methadone compared to 60 mg/day for subjects without U waves.

In conclusion, the results from this study suggest that maintenance doses of methadone and buprenorphine, commonly used in the United States and Australia for the treatment of opioid addiction, do not result in abnormally prolonged QTc intervals. However, there may be a dose-dependent effect. Given the association between U waves and cardiac arrhythmia, the prevalence of U waves in the higher dose methadone group is a matter of concern. Further research is required before conclusions should be drawn.

REFERENCES


