Effect of Buprenorphine and Antiretroviral Agents on the QT Interval in Opioid-Dependent Patients

Jennifer R Baker, Al M Best, Patricia A Pade, and Elinore F McCance-Katz

BACKGROUND: Cardiac arrhythmias have been linked to treatment with methadone and levacetylmethadol. HIV-positive patients often have conditions that place them at risk for QT interval prolongation including HIV-associated dilated cardiomyopathy, coronary artery disease as a consequence of highly active antiretroviral (ARV) therapy–associated metabolic syndrome, and uncorrected electrolyte abnormalities. As of February 14, 2006, no cases of adverse events related to QT interval prolongation have been reported in patients receiving buprenorphine, an opioid partial agonist and the newest drug approved for the treatment of opioid dependence.

OBJECTIVE: To evaluate the effects of buprenorphine/naloxone alone and in combination with 1 of 5 ARV agents (efavirenz, nelfinavir, delavirdine, ritonavir, lopinavir/ritonavir) on the QT interval.

METHODS: This study was prospective, open-label, and within-subject in design, with subjects serving as their own controls. In 50 HIV-negative, opioid-dependent subjects, electrocardiogram recordings were obtained at baseline, after receiving buprenorphine/naloxone for 2 weeks, and then following buprenorphine/naloxone plus ARV administration for 5–15 days at steady-state. QTc interval measurements were compared using mixed-model, repeated-measures ANOVA. Recent cocaine use and gender were considered covariates.

RESULTS: Buprenorphine/naloxone alone and often in the presence of evidence for recent use of cocaine did not significantly alter the QT interval (p = 0.612). Buprenorphine/naloxone in combination with ARVs caused a statistically, but not clinically, significant increase (p = 0.005) in the QT interval. Subjects receiving buprenorphine/naloxone in combination with either delavirdine or ritonavir had the greatest increase in QTc intervals.

CONCLUSIONS: Prolonged QT intervals were not observed in opioid-dependent subjects receiving buprenorphine/naloxone alone. QT interval increases were observed with buprenorphine/naloxone in combination with either delavirdine or ritonavir, which inhibit CYP3A4.

KEY WORDS: arrhythmias, buprenorphine, delavirdine, efavirenz, lopinavir, nelfinavir, ritonavir.

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Buprenorphine is a mu opioid-receptor partial agonist that has been shown to be as effective as methadone or levacetylmethadol (LAAM) for the treatment of opioid dependence.1-3 Like other mu agonists, buprenorphine produces typical opioid-associated subjective and physiologic effects, but its maximal effects are less than those of a full agonist and exhibit a ceiling effect.4 The most commonly prescribed buprenorphine product in the US is combined with naloxone, a mu opiate-receptor antagonist, and is given sublingually. Naloxone is poorly absorbed sublingually and does not alter buprenorphine opioid effects. However, the presence of naloxone limits diversion, because the opioid antagonist effects of naloxone predominate if the combination product is solubilized and injected.

Postmarketing LAAM surveillance contains reports of QT interval prolongation and arrhythmias, including life-threatening torsade de pointes, and led to removal of this product from the market. Cases of QT interval prolongation with high-dose methadone have also been cited, including reports among HIV-positive patients.5-9 As of February 14, 2006, no cases of adverse events related to QT interval prolongation have been reported in patients receiving buprenorphine. However, in vitro data suggest that buprenorphine is a potent inhibitor of cardiac human ether-a-go-go-related gene (HERG) potassium channels at concentrations higher than are therapeutically utilized.10 This gene has been proven useful for evaluating drugs causing delays in cardiac repolarization.

Highly active antiretroviral therapy (HAART) most commonly includes at least 3 antiretrovirals (ARVs; a pro-
tease inhibitor or nonnucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors). Protease inhibitors have been associated with blockade of HERG channels, therefore potentially predisposing individuals taking these medications to QT interval prolongation and torsade de pointes.11 HIV medications coupled with buprenorphine may exhibit an even greater risk of prolonging the QT interval than when these drugs are given independently.

This study reports the effect of buprenorphine/naloxone (CYP3A4 substrate), given alone or in combination with 1 of 5 ARVs with varying CYP3A4 impact, on the length of the QT interval in a population of opioid-dependent patients. This evaluation was part of a larger National Institutes of Health–funded study of drug interactions between opioids and HIV therapeutic agents.

**Methods**

**PARTICIPANTS**

Individuals were enrolled in this study if they were (1) HIV seronegative by antibody enzyme-linked immunosorbent assay prior to receiving any HIV medication, (2) 18 years of age or older, (3) not treated with drugs that alter CYP450 function or prolong the QT interval, and (4) without clinically significant medical conditions or significant abnormalities in blood cell indices, liver function tests, glucose, urea nitrogen, creatinine, and urinalysis. Subjects had to meet *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria for opioid dependence.12 Participants were started on buprenorphine/naloxone, and the dose was titrated to resolve opiate withdrawal symptoms and craving per clinical evaluation.

This study was approved by the Virginia Commonwealth University Institutional Review Board. Participants gave written informed consent prior to entering the study.

**DESIGN**

This study was prospective, open-label, and within-subject in design, with subjects serving as their own controls. Prior to buprenorphine/naloxone treatment, the QT interval for each subject was measured with lead II of the electrocardiogram (ECG) and corrected (QTc) for heart rate according to the method of Bazett.13 Buprenorphine/naloxone (average dose, mean ± SD, 16.3 ± 1.1 mg daily) was administered sublingually. After participants had been maintained on a stable dose of buprenorphine/naloxone for at least 2 weeks, an ECG, urine toxicology screen, and breath alcohol level were obtained. In addition to receiving buprenorphine/naloxone, subjects then began receiving 1 of the 5 ARVs at standard clinical doses for 5–15 days (nelfinavir 1250 mg twice daily for 5 days, lopinavir/ritonavir 400/100 mg twice daily for 7 days, ritonavir 100 mg twice daily for 10 days, delavirdine 600 mg twice daily for 7 days, efavirenz 600 mg daily for 15 days). The ritonavir dose is the low dose used for enhancing (boosting) protease inhibitor concentrations. Subjects received the ARV that was being evaluated at the time they entered the study. Duration of ARV therapy was chosen in an effort to achieve steady-state concentrations. Following this period, another ECG and urine toxicology screen were performed. All ECG measurements were obtained 2 hours after the morning dose of buprenorphine/naloxone and each ARV. All urine samples were tested for benzodiazepines, cannabis, cocaine, amphetamines, and opioids.

Subjects returned to the research unit daily to receive buprenorphine/naloxone and the ARV morning dose. Ingestion of these doses was observed by study staff to ensure adherence. The second ARV dose was given as a unit dose for take-home each day. Participants were required to return unit dose bottles and received a telephone call each afternoon from a member of the research staff to query about adverse events and remind them to take the afternoon dose of the ARV. Nelfinavir and delavirdine tablets were encapsulated with riboflavin. Riboflavin produces urine fluorescence and was used to monitor adherence to the study medication. Ritonavir and lopinavir/ritonavir could not be encapsulated because they are formulated as gelcaps. On day 3 (nelfinavir or delavirdine) or 4, participants received a urine test for fluorescence produced by riboflavin.

**DATA ANALYSIS**

QTc interval measurements at 3 time intervals were compared using mixed-model, repeated-measures ANOVA. JMP (version 5.0.5, SAS Institute, Cary, NC) software was used to analyze data. The basic unit of analysis was time interval, classified as baseline (subjects on no medication), buprenorphine/naloxone (after receiving the same dose for 2 wk), or buprenorphine/naloxone plus an ARV (after receiving the same ARV dose for 5–15 days, depending on the specific agent). The latter time intervals were chosen to record ECG measurements when drug concentrations were at steady-state. The response (dependent variable) was the QTc interval measurement. Main effects were considered statistically significant if the F ratios resulted in a p value of 0.05 or less (2-tailed). Significant main effects allowed for paired t-test comparisons of the 2 active groups (buprenorphine/naloxone, buprenorphine/naloxone plus an ARV) to baseline. If the time interval was significant, the difference between the time points was tested using a Bonferroni corrected p value of 0.025 or less. If an ARV had a significant effect, the difference between the time points for each drug was tested using the Bonferroni corrected p value of 0.005 or less.

A predetermined, clinically significant change in the QTc interval was established prior to study initiation. The QTc interval is considered prolonged if greater than 450 msec.14 Assuming a baseline of 400 msec, a difference must not be greater than 50 msec to be statistically equivalent. This was tested as an equivalence claim using 95% confidence intervals.15,16 Confidence intervals including an upper limit of 50 msec were considered clinically significant. With a sample size of 50, the study had greater than 99% power to reject an equivalence to within 50 msec, even if the standard error of the difference was as large as 2.8 msec.

**Results**

Ten subjects completed the study for each ARV medication. These people were 22–50 years of age (mean ± SD, 35.8 ± 7.9), weighed 61.5 to 112.7 kg (81.4 ± 15.7), and had been receiving a stable dose of buprenorphine/naloxone (range 16–20 mg; 16.3 ± 1.1) daily for at least 2 weeks. No participant required a change in the buprenorphine/naloxone dose during the study period. Twenty-six (52%) subjects were male. No subjects were receiving medications known to prolong the QT interval or had electrolyte abnormalities or impaired renal/hepatic clearance. All subjects had a normal heart rate (range 50–85 beats/min; 66.5 ± 1.6). None of the participants met diagnostic criteria for alcohol dependence or DSM-IV criteria for mental disorders. Twenty-five (50%) participants met
diagnostic criteria for cocaine use disorders, cocaine dependence, or cocaine abuse. Before QT interval measurements, urinalysis revealed recent cocaine use in 30 (60%) subjects at baseline, 18 (36%) subjects taking buprenorphine/naloxone, and 17 (34%) subjects taking buprenorphine/naloxone with an ARV. There was no difference in the numbers of cocaine-positive urine samples between the ARV groups ($\chi^2 = 4.99; p = 0.29$). By the participants’ reports, adherence to study drugs in which ingestion was not witnessed by staff was 100%, and subjects did not report any cardiac adverse advents. No participant reported any adverse event requiring medical intervention.

One baseline and one buprenorphine/naloxone plus lopinavir/ritonavir QT interval measurement were not collected. From the mixed-effect model, only the variable time interval was statistically significant ($F_{df} = 2.50; p = 0.008$). With this main effect finding, paired $t$-tests revealed that there was not a significant difference between QTc interval measurements at baseline versus those with buprenorphine/naloxone treatment ($p = 0.612$). A significant difference in QTc interval measurements was shown for baseline versus buprenorphine/naloxone plus ARVs ($p = 0.005$). Table 1 summarizes results from the mixed-effect model. Buprenorphine/naloxone in combination with delavirdine or ritonavir revealed the largest QTc interval measurement increases of 13.1 and 9.4 msec, respectively.

**Discussion**

We were unable to demonstrate QT interval prolongation effects of buprenorphine/naloxone alone at standard clinical dosages used in the treatment of opioid dependence. However, buprenorphine/naloxone in combination with ARVs was associated with a statistically significant increase in QTc intervals ($p = 0.005$). While this study did not reveal a statistically significant difference between various ARVs with respect to their ability to prolong the QT interval, Table 1 shows that delavirdine and ritonavir were associated with the largest increases in the QTc interval.

Confidence intervals for changes from baseline for each ARV did not include an upper bound of 50 msec, which had been predefined as indicating a clinically significant change. The study design was conservative in choosing 50 msec as the threshold for determining a clinically significant QTc interval increase, as clinical experts have suggested that an increase of greater than 60 msec from baseline indicates risk of arrhythmia.17,18 It is notable that delavirdine and ritonavir resulted in the largest QTc interval measurement increase from baseline and have the largest upper confidence bounds (Table 1).

Delavirdine or ritonavir alone may have been responsible for the observed QT interval prolongations. However, the combination of one of these drugs with buprenorphine may increase the QT interval because these ARVs increase buprenorphine plasma concentrations.19 When lopinavir/ritonavir was given with buprenorphine, the same QT interval prolongation observed with the ritonavir and buprenorphine combination did not occur. This may be due to the lack of increased buprenorphine exposure when these agents are administered simultaneously.19 Ritonavir alone is an inhibitor of CYP3A4; lopinavir and the combination product lopinavir/ritonavir may be associated with enzyme induction.20

While the results from this study indicate that the increased duration of the QT interval seen with delavirdine or ritonavir in combination with buprenorphine/naloxone

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>n</th>
<th>Least-Squares Mean QTc, msec (SE)</th>
<th>Mean Change From Baseline, msec (SE)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>49</td>
<td>409 (2.6)</td>
<td></td>
<td></td>
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<tr>
<td>Buprenorphine</td>
<td>50</td>
<td>410 (2.6)</td>
<td>1.41 (3.24)</td>
<td>−4.94 to 7.76</td>
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<tr>
<td>Buprenorphine + ARV</td>
<td>49</td>
<td>417 (2.7)</td>
<td>8.15 (3.28)</td>
<td>−1.72 to 14.58</td>
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<tr>
<td>Baseline QTc by ARV assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>delavirdine</td>
<td>10</td>
<td>410 (5.8)</td>
<td></td>
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<td>efavirenz</td>
<td>9</td>
<td>408 (6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>10</td>
<td>407 (5.8)</td>
<td></td>
<td></td>
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<tr>
<td>nelfinavir</td>
<td>10</td>
<td>411 (5.8)</td>
<td></td>
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<tr>
<td>ritonavir</td>
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<tr>
<td>delavirdine</td>
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<td>423 (5.9)</td>
<td>13.12 (5.94)</td>
<td>1.48 to 24.76</td>
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<td>6.14 (6.18)</td>
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<td>418 (5.8)</td>
<td>6.72 (5.94)</td>
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<tr>
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<td>419 (5.9)</td>
<td>9.38 (5.99)</td>
<td>−2.36 to 21.12</td>
</tr>
</tbody>
</table>

ARV = antiretroviral.  
*Baseline versus buprenorphine plus ARV; p = 0.005.*
was not clinically significant, it is not known whether continued administration of these drug combinations will result in even greater buprenorphine accumulation that may lead to further QT interval increases. Therefore, clinicians may want to consider obtaining ECGs when clinically indicated in patients receiving buprenorphine/naloxone and HAART containing ARVs that may inhibit hepatic drug metabolism.

The current number of medications and variety of interactions leading to QT interval prolongation is daunting and has been an increasing problem in treating opioid-dependent patients. Data from prospective clinical trials are rarely available to determine whether a drug alone or in combination with other drugs will cause QT interval prolongation before a case report arises. This has led the Food and Drug Administration to develop a draft document that provides recommendations on conducting thorough QT/QTc interval studies early in the clinical development of non-antiarrhythmic drugs. The current draft states that a drug causing a mean QTc interval measurement change from baseline of 5 msec or less with an upper-bound confidence interval of 8 msec is “so small as to be of no consequence.” After subjects in our study had been receiving a mean dose of 16/4 mg of buprenorphine/naloxone daily for at least 2 weeks, the mean change in QTc interval measurement from baseline (ie, when subjects were taking no medication) was a small increase of 1.41 msec, with an upper-bound confidence interval of less than 8 msec underscoring the lack of effect of buprenorphine alone on the QT interval.

Women were well represented in this study (48%), and QT interval changes were not shown to be significantly related to gender (p = 0.20). Still larger QT/QTc interval studies in women who are prescribed buprenorphine/naloxone would be illuminating, as women have a higher risk for QT interval prolongation resulting in torsade de points. When receiving buprenorphine/naloxone, a large percentage (36%) of subjects in this study showed evidence of recent cocaine use. Cocaine has long been recognized as cardiotoxic by blocking sodium and potassium channels and depressing cardiac function, and its use has been associated with episodes of torsade de points as well as myocardial infarction. While this study was not designed to directly assess the potential cardiotoxicity of cocaine and buprenorphine/naloxone in combination, the results provide no evidence (p = 0.44) that buprenorphine/naloxone treatment adds to the cardiotoxic effects of cocaine.

There are several limitations to this study. First, Bazett’s correction was used to normalize QT interval recordings based on heart rate. For accurate interpretation, Bazett’s correction requires heart rates between 50 and 75 beats/min. This formula under-corrects for low heart rates and over-corrects for elevated heart rates. The majority (31%) of heart rates in our population that were out of that range were above 75 beats/min. Therefore, QT intervals may have been over-corrected for these measurements. Only one (1%) heart rate was below 50 beats/min.

This study was performed in opioid-dependent subjects without HIV disease. HIV patients who are treated with buprenorphine/naloxone in addition to their HAART regimens may have other factors that place them at risk for QT interval prolongation that HIV-negative patients may not possess. Patients with HIV are also taking multiple medications that can prolong the QT interval. In the current study, we only evaluated the QT interval effect of one ARV at a time in combination with buprenorphine/naloxone. This is a limitation in the sense that HIV patients are always on multiple medications, but the design is also necessary to determine which drugs are more likely to be associated with prolongation of the QT interval.

Finally, the design of the study did not allow us to fully differentiate whether the observed QT interval prolongation was the result of a pharmacokinetic interaction, a pharmacodynamic interaction, or their combination. Future studies should be designed to obtain serial ECG measurements at the same time ARV and buprenorphine plasma concentrations are sampled.

Conclusions

Buprenorphine/naloxone alone treatment did not alter QTc intervals. Therefore, this combination might offer an advantage over methadone maintenance therapy in opioid-dependent patients at a lower risk for prolongation of the QT interval. Buprenorphine/naloxone in combination with ARVs caused a statistically significant increase in the QT interval, which is not likely to be clinically significant. However, this study examined effects on the QT interval following relatively short periods of ARV administration.

Individuals receiving buprenorphine/naloxone for opioid dependence and who require chronic treatment with ARVs that inhibit metabolism of buprenorphine, such as ritonavir or delavirdine, may be more prone to lengthening of the QT interval. Additional studies examining the effect of buprenorphine/naloxone on ARVs will help to clarify whether risk for arrhythmia is increased when these drugs are administered concomitantly.

Jennifer R Baker PharmD MS, Postdoctoral Research Fellow, Addiction Psychiatry, Virginia Commonwealth University, Richmond, VA
AI M Best PhD, Associate Professor, School of Public Health, Virginia Commonwealth University
Patricia A Pade MD, Assistant Clinical Professor, Addiction Psychiatry, School of Medicine, Virginia Commonwealth University
Elinore F McCance-Katz MD PhD, Professor and Chair, Addiction Psychiatry, School of Medicine, Virginia Commonwealth University
Reprints: Dr. McCance-Katz, Division of Addiction Psychiatry, West Hospital, 1200 E. Broad St., Rm. 1142, Richmond, VA 23298-0109, fax 804/828-5386, emccancekatz@vcu.edu
CONCLUSIONS: No se observó alargamiento del segmento QT en pacientes dependientes de opíaceos tratados con buprenorfina/naloxona. Se observó un alargamiento del segmento QT cuando se combinó la buprenorfina/naloxona con delavirdina o ritonavir, fármacos inhibidores del CYP3A4 hepático.

Mitchell Nazario

RÉSUMÉ

INTRODUCTION: Certaines arythmies cardiaques sont associées à la méthadone et au levacetylméthadol. Les patients avec le VIH ont souvent des conditions médicales qui les prédisposent à une prolongation de l’intervalle QT telles la cardiomyopathie dilatée associée au VIH, la maladie coronarienne secondaire à un syndrome métabolique due à une thérapie antirétrovirale hautement active et diverses anomalies electrolytiques. Jusqu’à maintenant, aucun cas de prolongation de l’onde QT n’a été rapporté chez les patients recevant la buprénorphine, un agoniste opiacé partiel indiqué dans le traitement de la dépendance aux opiacés.

OBJECTIF: Évaluer les effets de la buprénorphine/naloxone seule et en combinaison avec 1 des 5 antirétroviraux (éfavirenz, nevirapine, delavirdine, ritonavir, lopinavir/ritonavir) sur l’intervalle QT.

MÉTHODOLOGIE: Cette étude prospective, ouverte, et en chassé croisé a été effectuée auprès de 50 patients VIH négatif et dépendant d’opiacés. Des électrocardiogrammes ont été obtenus au moment de la thérapie, après avoir reçu la buprénorphine/naloxone pour 2 semaines et ensuite après avoir reçu la buprénorphine/naloxone et un antirétroviral pour 5–15 jours jusqu’à l’état d’équilibre. Les valeurs de QT corrigé furent comparées par analyse de variance pour mesures répétées. L’utilisation récente de cocaine et le sexe furent considérés comme co-variabes.

RÉSULTATS: La buprénorphine/naloxone seule et en présence d’une utilisation récente de cocaine n’a pas modifié l’intervalle QT (p = 0.612). La buprénorphine/naloxone en combinaison avec un antirétroviral a causé une augmentation statistiquement mais non cliniquement significative (p = 0.005) de l’intervalle QT. Les sujets recevant la buprénorphine/naloxone en combinaison avec la delavirdine ou le ritonavir ont subi les augmentations les plus importantes du QTc.

CONCLUSIONS: Un intervalle QT prolongé n’a pas été observé chez les patients dépendants d’opioïdes et recevant la buprénorphine/naloxone seule. Les augmentations d’intervalle QT furent observées avec la buprénorphine/naloxone en combinaison avec la delavirdine ou le ritonavir, des substances inhibitrices du CYP3A4.

Marc M Perreault