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Longitudinal ECG changes in cocaine users during extended abstinence

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Abstract

Background—Cocaine lengthens electrocardiographic QTc, QRS and PR intervals through blockade of sodium and potassium channels, but changes during withdrawal have not been well studied.

Methods—We recorded weekly electrocardiograms (ECGs) from 25 physically healthy cocaine users (84.0% men, mean [S.D.] age 34.7 [4.1] years, 9.0 [5.2] years of cocaine use, 9.4 [3.5] days of use in the 2 weeks prior to admission) over 3 months of monitored abstinence on a closed ward. Subjects had minimal current use of other drugs. Baseline ECGs were recorded 20.5 h [16.6] after last cocaine use.

Results—Baseline QTc interval correlated positively with total amount of cocaine used and amount used per day in the 2 weeks prior to ward admission. There was a significant 10.5 ms [12.9] shortening of QTc interval during the first week of withdrawal, with no further significant changes thereafter. There were no significant changes in PR or QRS intervals.

Conclusions—These findings suggest that cocaine-associated QTc prolongation returns toward normal during the first week of cocaine abstinence.

Keywords

Cocaine; ECG; Withdrawal; QTc; Longitudinal; Abstinence

1. Introduction

Acute cocaine use transiently lengthens electrocardiogram (ECG) parameters of PR, QRS and QTc intervals (Erwin and Deliargyris, 2002). Effects of extended cocaine abstinence after chronic cocaine exposure are less well understood. We know of only one study of ECG parameters during cocaine withdrawal, which found that PR interval lengthened over 30 days of cocaine withdrawal (Kajdasz et al., 1999). QTc interval and QRS duration remained unchanged. That study was cross-sectional, assessed withdrawal status largely by subject self-report, and evaluated only three time points.

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Conflict of interest: None.

The present study evaluated ECG data collected longitudinally over 3 months in 25 chronic cocaine users undergoing monitored abstinence.

2. Methods

2.1. Subjects

Twenty-five cocaine users with current abuse/dependence (DSM-IV criteria (American Psychiatric Association, 1994)) participated in a study of cocaine withdrawal (Gorelick et al., 2005; Levin et al., 2007). The study was approved by the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) and Johns Hopkins Bayview Medical Center institutional review boards. Subjects gave written informed consent and were paid for their participation.

Subjects received comprehensive medical and psychological screening. Eligibility criteria included no clinically significant abnormality; no current use of prescription medications; cocaine use averaging ≥ 1 g/week for 3 months; urine toxicology positive for cocaine and negative for other drugs; no current psychiatric or substance use disorder other than cocaine or tobacco. Data on substance use was collected at weekly visits prior to ward admission using the timeline follow-back method (Sobell and Sobell, 1992), confirmed with urine drug tests.

2.2. Procedures

Standard 12-lead ECGs were recorded during screening, within 2 days of admission to the NIDA-IRP closed research ward (Week 0 baseline), then weekly. To prevent use of unauthorized drugs on the ward, no passes or visitors were allowed, all personal belongings and mail were screened, and random urine samples were tested for drugs. No medications were administered except over-the-counter drugs. Seventeen subjects remained on the ward for 3 months; six stayed for 3 weeks; two stayed for 2 weeks, then returned daily for a week with urine drug screens at each visit. Twenty-two subjects received 1–4 intranasal cocaine doses (40–180 mg) on the ward (admission day, after 1 week, after 11 weeks). ECG recordings were obtained before cocaine administration on dosing days.

2.3. ECGs

Resting ECGs were recorded with a Marquette Mac[®]VU electrocardiogram (Marquette Electronics, Milwaukee, WI). Parameters analyzed included PR interval, QRS interval, QT and QTc duration and heart rate. QTc duration was calculated using Bazett's formula: $QTc = QT / \sqrt{(inter - beat \text{ interval})}$.

2.4. Statistical method

Each dependent variable was analyzed with repeated-measures linear regression (Proc Mixed, SAS 9.1, SAS Institute, Cary, NC); the independent variable was Week (0–12). Each week was compared with baseline using the Dunnett–Hsu method. The two-tailed alpha was 0.05. Descriptive statistics and correlational analyses used SPSS v.13.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Subject characteristics

Subjects (21 males, 4 females) had a mean [S.D.] age of 34.7 [4.1] years, used cocaine regularly for 9.0 [5.2] years and used on 9.4 [3.5] of the 14 days prior to admission. Last cocaine use was 20.5 h [16.6] prior to baseline ECG. Subjects used alcohol on 2.2 [3.1] days and marijuana on 0.4 [0.8] days in the 2 weeks prior to admission; 15 were tobacco smokers.

3.2. ECG results

All ECG parameters for all subjects were within normal limits. There was significant shortening of QTc interval ($p = 0.004$), due to a 10.5 ms [12.9] shortening from baseline to Week 1 ($p = 0.0008$) (Fig. 1). Eighteen subjects shortened QTc from baseline to Week 1, six increased, and one showed no change. QTc values ranged from 382 ms to 467 ms at baseline and from 372 ms to 416 ms at Week 1. There was a trend toward QTc lengthening at Week 11 ($p = 0.16$) (Fig. 1).

Baseline QTc interval had a significant positive correlation with total amount spent on cocaine in the 2 weeks prior to ward admission ($p = 0.02$) and with average amount of cocaine used per day of use ($p = 0.04$). There was no significant correlation between baseline QTc interval and hours since last cocaine use ($p = 0.54$).

There was a significant shortening of the QT interval ($p < 0.0001$), due to significant shortening between baseline and Weeks 1–5 (all p -values < 0.05) (Fig. 1). There was a 26.8 ms [22.3] shortening between baseline and Week 1.

There was no significant overall change in heart rate ($p = 0.18$) (Fig. 1). There was a significant 7.5 bpm [10.5] heart rate increase between baseline and Week 1 ($p < 0.01$). Seventeen subjects increased heart rate from baseline to Week 1; eight subjects decreased.

There were no significant changes in PR interval ($p = 0.26$) or QRS duration ($p = 0.23$) (data not shown).

Seventeen subjects had ECGs at follow-up, 14 of whom had resumed cocaine use (based on urine testing) during their mean follow-up interval of 16.1 (18.0) days (range 5–58 days). The 14 subjects who relapsed during follow-up differed from the 11 who did not in years of cocaine use (11.1 [5.1] vs. 6.2 [4.0] [$p = 0.01$]) and age (36.3 [3.0] years vs. 32.6 [4.5] years [$p = 0.03$]). Among the 14 subjects who relapsed, there was no significant difference between their final ECG on the ward and first ECG after relapse for any parameter (all p -values > 0.05 ; data not shown). Subjects who relapsed used cocaine 37.0% [25.9%] of days with available data, and spent \$46.03 [\$47.80] on cocaine per day of use after discharge.

4. Discussion

We observed a significant shortening of both the uncorrected QT and QTc intervals in cocaine-using subjects undergoing 3 months of monitored cocaine abstinence. Most change occurred during the first week (Fig. 1). No changes occurred in either PR interval or QRS duration. These findings are largely inconsistent with the one prior published study (Kajdasz et al., 1999), which reported a shortening of PR interval, but no change in QTc interval or QRS duration.

Several factors may account for the different findings. First, the prior study relied largely on retrospective self-report to assess cocaine abstinence; subjects may have misreported their abstinence. Second, given the cross-sectional design, ECG differences among subjects may have obscured a withdrawal effect. Third, in the prior study, subjects using cocaine only once in the prior month could be included; the “immediate abstinence” time point included subjects who reported no cocaine use for ≤ 5 days prior to their ECG (mean interval 2.9 [1.4] days). In contrast, the present study required cocaine use averaging ≥ 1 g/week for the prior 3 months and recorded baseline ECGs within 20.5 h (16.6) of last cocaine use. Thus, subjects in the prior study may have used less cocaine in the preceding months and had a longer duration of abstinence than subjects in the present study. This might have produced less effect on QTc interval at baseline, giving less opportunity to see shortening during abstinence.

Our results are consistent with the hypothesis that QTc interval should shorten during cocaine withdrawal, as cocaine-induced QTc interval lengthening (Gamouras et al., 2000) attenuates. This interpretation is consistent with the observed significant positive correlations between baseline QTc interval and measures of cocaine use in the 2 weeks prior to admission.

There was a non-significant trend ($p = 0.16$) toward QTc lengthening at Week 11 (Fig. 1) whose mechanism, assuming it is a true phenomenon, is unclear. It is unlikely to be due to resumed use of cocaine or other substances, given the secure arrangements on the ward. It could be related to subjects' anticipation of a forthcoming cocaine challenge (for seven subjects) or of discharge from the ward in the following 1–2 weeks.

The first post-relapse ECG after ward discharge was not significantly different from the final ECG on the ward. This suggests that short-term levels of cocaine use (37% of days over ~2 weeks) were not sufficient to prolong QTc interval. However, this interpretation is tentative because of low statistical power: 12.5% to detect an ECG change comparable to that observed between baseline and Week 1 (DSS Research, 2007).

There was no overall significant change in heart rate, but a significant increase was seen between baseline and Week 1 (Fig. 1). This is consistent with prior studies examining heart rate. Weddington et al. (1990) showed an increase of ~10 bpm over the first week of monitored abstinence on a research ward, followed by a stable heart rate over the subsequent 3 weeks. The relative bradycardia seen immediately after cessation of cocaine use may reflect desensitization or tolerance to its tachy-cardic effect because of extended cocaine use (Weddington et al., 1990).

QTc interval shortening between baseline and Week 1 occurred in the context of increased heart rate. An increased heart rate (lower inter-beat interval) lengthens the QTc interval under the Bazett formula, assuming QT interval is unchanged. Thus, a shortened QTc interval despite an increased heart rate implies a substantial change in cardiac repolarization, as evidenced by the significant shortening of QT interval between baseline and Week 1 (Fig. 1). This pattern of findings supports the electrophysiological significance of the observed QTc change.

This study has several strengths. It is the first published study we know of that used a prospective, longitudinal design to examine the effects of cocaine withdrawal on electrocardiographic parameters, with withdrawal being ensured by subjects residing on a closed research ward. It recorded ECGs weekly over 3 months, allowing evaluation of time course. Subjects were primary cocaine users, with minimal current use of other substances. Thus, the observed ECG changes were almost certainly due to cocaine withdrawal, rather than to effects of other substances.

This study had several limitations, including small sample size and limited external validity. Subjects had minimal use of drugs other than cocaine and were physically and psychologically healthy, making them atypical of most cocaine users seen in clinical settings. Twenty-two subjects received 1–4 intranasal cocaine doses (40–180 mg) during their stay on the research ward, but it is unlikely that these influenced the ECG data. ECG recordings on dosing days took place before cocaine administration; no ECG recording occurred less than a week after the preceding cocaine dose. This temporal sequence, plus the relatively low intranasal doses administered, makes it unlikely that administered cocaine altered the pattern of ECG changes.

Although the screening of subjects for cardiovascular conditions revealed no clinically significant abnormalities (including no evidence of structural heart disease), it is possible that some subjects had undetected cardiac abnormalities. We consider it unlikely that any such undetected abnormality would have significantly influenced our electrophysiological findings.

Another study limitation is changing sample sizes and different subsets of subjects contributing data at various time points, due to dropouts and missing data. We do not believe that these factors substantially affect the validity of our findings. First, the SAS Proc Mixed procedure is designed to accommodate fluctuating sample sizes and missing data. Second, two additional analyses using consistent sample sizes over time gave similar results as the original analysis (data not shown): eight subjects with complete data (except for Week 10) and 19 subjects with a complete first 3 weeks of data.

Our findings have implications for clinical practice. While the primary treatment for cocaine-associated cardiovascular abnormalities is abstinence, it may be helpful for clinicians to know what ECG changes to expect over what time course in chronic cocaine users entering treatment, especially when medications known to affect ECG parameters may be involved in the treatment. Although the absolute magnitude of QTc interval change was small, our findings suggest that 1 week of cocaine abstinence may be sufficient to resolve any cocaine-associated QTc prolongation, a risk factor for cardiac arrhythmias and sudden death (Gamouras et al., 2000). They also imply that a minimum degree of regular cocaine use must be resumed before significant changes in the QTc interval return. Future research with larger and more varied samples of cocaine users, more frequent measures during early withdrawal, and objective measures of cocaine use (e.g., benzoylecgonine levels) is needed to better address these issues.

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Fig. 1.

QTc and heart rate changes over up to 12 weeks of monitored abstinence in 25 adult cocaine users. Twelve-lead, resting ECGs were done after admission to a closed research ward (mean [S.D.] of 20.5 h [16.6] after their cocaine use), then weekly for up to 12 weeks (3 weeks for eight subjects). QTc was calculated using Bazett's correction ($QTc = QT / \sqrt{RR}$). There was significant overall QTc change ($p < 0.01$, by repeated-measures linear regression) and significant QTc shortening between admission (Week 0) and Week 1 ($p < 0.001$, by Dunnett-Hsu method for multiple comparisons). There was a significant overall change in QT ($p < 0.0001$) and significant QT shortening between admission (Week 0) and Weeks 1 ($p < 0.0001$), 2 ($p < 0.01$), 3 ($p < 0.01$), 4 ($p < 0.05$), 5 ($p = 0.05$) and 8 ($p < 0.05$). There was also a significant increase in heart rate from admission (Week 0) to Week 1 ($p < 0.01$). Week 13 is not depicted because of small sample size ($n = 2$) (* $p < 0.05$ for change from admission).