BRIEF ORIGINAL

QTc prolongation in patients with symptoms of cocaine use

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None

Objetive: To assess the presence of QTc prolongation in emergency department patients with symptoms of cocaine intoxication and to determine whether QTc prolongation correlated with benzoylecgonine level.
Methods: The records of all patients coming to the emergency department with symptoms of cocaine intoxication in 2009 were reviewed to collect data on age, sex, and use of drugs that could cause QTc prolongation A QTc interval longer than 450 milliseconds was considered prolonged. Benzoylecgonine levels were also recorded. A group of nonusers of cocaine were used as controls.
Results: Data for 44 cases and 18 controls were included. The QTc interval was prolonged in cocaine users (445.7 milliseconds vs 411.1 milliseconds in nonusers; *P*<.001). A higher percentage of cases had QTc prolongation (59.1% vs 16.7% of the controls; *P*=.002). Benzoylecgonine level and QTc duration were not correlated. Nine patients were in treatment with drugs that could cause QT interval changes. However, QTc duration did not differ between these patients and others who were not taking those drugs; nor were the percentages of QTc interval disturbances different between these 2 patient groups.
Conclusions: Cocaine use causes QTc prolongation and is associated with more observations of pathologically prolonged intervals. The differences are not influenced by medications that also prolong the QT interval. Benzoylecgonine level and QTc duration are not correlated. [Emergencias 2012;24:289-291]

Key words: Cocaine. QTc interval. Benzoylecgonine.

Introduction

Cocaine use increased until 2005[1,2]; since then it declined in students aged 14-18 years and has stabilized in the population aged 15-64 years[3]. Of the illegal drugs, cocaine generates the highest rate of health problems[3], accounting for 28.6-66% of all emergency department (ED) visits for substance abuse[4,5]. Cocaine use is more frequent in males[5] regardless of the origin of the population attended[6]. Cardiovascular complications arising from cocaine use are known[7], but it is not known whether there is a correlation between electrocardiographic manifestations and cocaine metabolite levels.

The objectives of this study were to determine QTc interval prolongation in the ECG that cocaine produces, compared with a group of non-user volunteers, to determine whether the use of other drugs that potentially cause QT interval prolongation influences QTc prolongation and to determine whether the latter correlates with levels of benzoylecgonine, the primary metabolite of cocaine.

Method

We included patients attended in the emergency department (ED) for health problems related with cocaine consumption in 2009. Consumption was considered to have taken place when thin layer chromatography urine analysis proved positive (cutoff point of 300 ng/ml benzoylecgonine) or when the patient admitted to having consumed cocaine. We collected data on age, sex, consumption of drugs that potentially cause QT interval prolongation[8], and a urine sample and 5 ml of blood for the determination of benzoylecgonine. ECG was performed after sample collection. The QT interval was measured manually. Heart rate was adjusted to obtain QTc values using Bazett's formula.

A QTc value greater than 450 msec was considered as prolonged. The determination of benzoylecgonine in urine and plasma was performed using an automatic analyzer (Living System, by Siemens). The test used for cocaine metabolite detection was Emit® II Plus, a homogeneous enzyme immunoassay with a cutoff of 150 ng/mL [SAMHSA (Substance Abuse and Mental Health Services Administration) cutoff level confirmatory test].

A control group was formed of healthy volunteers recruited from hospital workers, matched for age and sex with the cases, who reported never having used cocaine, and they underwent an ECG at baseline.

Comparisons of QTc were made between groups and analyzed to determine whether the use of other drugs that potentially cause QT interval prolongation influenced these measurements. We analyzed whether there was a correlation between benzoylecgonine levels and QTc measurements.

All statistical analyses were performed using SPSS vs 15. Student's t test was used to compare mean values, and chi-square with Fisher correction when necessary for the comparison of proportions. Correlations were determined using Spearman's test.

Results

The study included 44 patients (34 positive qualitative test and 10 admitting consumption) and 18 controls. Mean patient age was 33.7 (± 9.6) years vs controls 32.9 (± 7.8) years; 72.7% of consumers were males, compared to 61.1% of controls. Patient symptoms motivating the ED visit are listed in Table 1.

Fifteen patients (34.1%) had associated alcohol, 10 (22.7) heroin, 2 (4.5%) benzodiazepines, 2 (4.5%) MDMA (amphetamine derivatives, known as ecstasy) and 2 (4.5%) GHB (gamma-hydroxybutyric acid or liquid ecstasy). Average stay in the ED was 13.82 (±11.2) hours and 31 patients (70.45%) required observation for more than 6 hours.

Table 1. Clinical symptoms in patients consulting the ED for health problems related with the consumption of cocaine

	Symptoms n (%)
Chest pain	9 (20)
Palpitations	4 (9)
Dyspnea	4 (9)
Seizure	4 (9)
Gastrointestinal symptoms	3 (7)
Anxiety	8 (18)
Psychomotor agitation	10 (23)
Decreased awareness	16 (36)
Others*	4 (9)

*One case of lightheadedness, one ataxia and loss of muscle tone, one headache and one painful upper left extremity.

Consumer heart rate was greater [89.8 (± 22.3) vs controls 72.2 (± 14.7) bpm; P = 0.001], and consumer QTc intervals were more prolonged (445.7 vs controls 411.1 msec; P < 0.001). The percentage of pathologically prolonged QTc was significantly higher in the consumers (59.1% vs 16.7%; P = 0.002). No differences were found in PR and RR intervals or duration of QRS. All were in sinus rhythm. Anterosuperior block was observed in 4 patients and 1 control. There were negative T waves in 5 patients (none in controls) and peaked T waves in 3 cases and 2 controls. No patient had severe arrhythmia or sudden death syndrome. One consumer was diagnosed with STEMI and two with probable coronary vasospasm.

Regarding the most important analytical parameters for the genesis of arrhythmia, sodium (Na) and potassium (K) in plasma were within reference ranges in all cases [141 (3.6) mEq/l and 4.1 (0.4) mEq/l]. Mean pH and bicarbonate were also normal [7.37 (0.08) and 25.89 (3.7) mEq/l] and only one patient had metabolic acidosis.

Nine patients were being treated with drugs that may alter the QT interval[8,9] (Table 2). There were no differences in mean QTc based on this factor [446.8 (27.6) vs 445.3 (42.2) ms], nor in the percentage of pathological QTc (55.5% vs 60%). Restricting the analysis to those patients taking other drugs with known potential for QT alteration8, not only based on their potential (three methadones), no differences were found.

No correlation was found between levels of benzoylecgonine in plasma and urine and the duration of QTc (data not shown).

Discussion

These results show that cocaine use was directly associated with prolonged QTc interval, regardless of the consumption of other drugs that potentially prolong QT. However, levels of

Table 2. Other drugs that potentially cause QT interval prolongation taken by 9 patients consulting the ED for health problems related with the consumption of cocaine

	Drug 1	Drug 2
Patient 1	Olanzapine	
Patient 2	Methadone	
Patient 3	Olanzapine	
Patient 4	Lopinavir	Ritonavir
Patient 5	Olanzapine	Quetiapine
Patient 6	Paroxetine	
Patient 7	Thiethylperazine	
Patient 8	Methadone	
Patient 9	Methadone	

benzoylecgonine did not correlate with the duration of QTc. Cocaine use is associated with multiple cardiovascular alterations, which can lead to sudden death[7]. Arrhythmias are produced by a blocking effect on Na channels[10] and by increased circulating catecholamines, which produces tachycardia and increases Na channel blockade18. Blockade of K channels cannot be ruled out as causes of arrhythmia[11].

Intravenous administration of cocaine produces a variation of dose-dependent QT[12]. The importance of measuring QTc is that it allows identification of patients at risk of developing malignant arrhythmias, one of the first signs of myocardial ischemia[13]. The primary metabolite of cocaine is benzoylecgonine, which can be determined in blood within 5-15 minutes and in urine after 20 minutes of consumption[14].

This study confirmed QTc prolongation, but there were no ventricular arrhythmias or any case of sudden death. The absence of arrhythmias may be because they are favored by acidosis[10], present only in a patient. However, the acid-base balance could be useful for decision making. Furthermore, QTc prolongation was independent of consumption of other drugs. One patient included in the analysis was also being treated with protease inhibitors, despite the controversy surrounding its effect on QT[15].

The main limitations of this study are the small number of patients, the fact that it was conducted in a single center, and the use of other drugs that potentially prolong QTc, although analysis of this subgroup showed no differences with respect to those patients who only used cocaine.

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Alargamiento del intervalo QTc en pacientes con síntomas relacionados con el consumo de cocaína

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Objetivo: Determinar si el consumo de cocaína produce alargamiento del intervalo QTc y si se correlaciona con los niveles de benzoilecgonina.
Método: Estudio de los pacientes que consultaron en urgencias por síntomas relacionados con el consumo de cocaína durante el año 2009. Se recogió edad, sexo y consumo de fármacos potencialmente alargadores del intervalo QT. Se consideró alargado un QTc superior a 450 msg. Se realizaron niveles cuantitativos de benzoilecgonina. Se utilizó un grupo control de no consumidores de cocaína y se determinaron las diferencias entre los dos grupos.
Resultados: Se recogieron 44 casos y 18 controles. El QTc estaba más alargado en los consumidores (445,7 *vs* 411,1 mseg; p < 0,001). El porcentaje de QTc patológicamente alargados fue superior en los consumidores (59,1% *vs* 16,7%; p = 0,002). No se encontró correlación entre los niveles de benzoilecgonina y la duración del QTc. Nueve pacientes estaban en tratamiento con fármacos con posibilidad de alterar el QT. No se encontraron diferencias entre el QTc de estos casos y el de los que no tomaban dichos fármacos, así como tampoco en el porcentaje de QTc patológicos.
Conclusiones: El consumo de cocaína produce alargamiento del QTc, así como mayor porcentaje de QTc patológicamente largos. Estas diferencias no se ven influenciadas por la toma de fármacos alargadores del QT. No se ha encontrado correlación entre los niveles de benzoilecgonina y la duración del QT. [Emergencias 2012;24:289-291]

Palabras clave: Cocaína. QTc. Benzoilecgonina.