

ECG changes amongst patients with alcohol withdrawal seizures and delirium tremens

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Summary

Introduction: Alcohol withdrawal seizures and delirium tremens (DT) are serious complications of alcohol dependence. The prevalence of arrhythmias and other electrocardiographic (ECG) changes occurring in these clinical situations is not well studied.

Methods: We performed a retrospective analysis of clinical data and ECG's from patients discharged between 1995 and 2005 with the diagnosis of DT (ICD-Code F10.4) or alcohol withdrawal seizures (F10.3). Measurement of the ECG intervals was done in lead II. The corrected QT interval (QTc) was obtained using Bazett's formula.

Results: 49 patients (38 males; 11 females) with a mean age of 48 years were included in the study. 23 patients with DT and 16 with convulsions were admitted to the hospitals. Ten patients developed DT while being hospitalised for other reasons. The QTc interval was prolonged (>440 ms and

>460 ms in males and females, respectively) in 31 patients (63%). Five patients (10%) developed tachyarrhythmias (two torsade de pointes, one sustained ventricular tachycardia, two supraventricular tachycardia, one atrial fibrillation). All returned to sinus rhythm after appropriate treatment.

Conclusions: Tachyarrhythmias are common amongst patients with severe alcohol withdrawal syndromes. The majority of the patients had an acquired long QT syndrome which led to a torsade de pointes in two cases. No patient died in the hospital and all were discharged in sinus rhythm. Clinicians should possibly avoid QT prolonging drugs and carefully monitor the rhythm in patients with severe alcohol withdrawal syndromes.

Key words: QT-prolongation; ventricular tachycardia; alcohol withdrawal

Introduction

Alcohol dependence is a common problem, being diagnosed in up to 25% of hospitalised patients [1]. Depending on the screening tool the prevalence may vary [2]. In Switzerland, the diagnosis of "alcohol dependence" defined as ICD-Code F10.2 was established in 5% of male patients and in 1.7% of female patients hospitalised in 2002 [3].

Alcohol withdrawal is among the many medical problems associated with alcohol dependence. Minor symptoms of alcohol withdrawal can include insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations or anorexia [4].

A small proportion of alcohol-dependent men and women experience delirium tremens (DT) and/or convulsions during alcohol withdrawal [5]. These symptoms occur within 2–3 days after cessation of alcohol intake [4]. Abrupt cessation of alcohol drinking unmasks compensatory overac-

tivity of the nervous system and increased levels of several neurotransmitters such as gamma-aminobutyric acid (GABA), norepinephrine and serotonin have been noted [4, 6–9]. The effects of these neurotransmitters are not limited to the brain and effects on the cardiovascular system, especially the heart seem likely [6, 10, 11].

Little is known about electrocardiographic changes and the prevalence of dangerous ventricular arrhythmias in alcohol withdrawal syndromes [12]. Otero-Anton et al. documented a prolonged QTc interval in 46.8% patients during alcohol withdrawal syndrome [13]. Only patients with mild withdrawal symptoms were included and no dangerous arrhythmias were reported. A case report has described that following alcohol withdrawal by an alcohol-addicted mother, her newborn developed ventricular tachycardia on the 3rd day and had a prolonged QT interval that sub-

sequently normalised [14]. Early studies found DT mortality to be as high as 15%, but with advanced treatment more recent studies indicate mortality of 0 to 1% [15, 16].

Following our documentation of a torsade de

pointes arrhythmia in a patient we aimed to analyse the prevalence of arrhythmias and other important electrocardiographic changes amongst patients with severe alcohol withdrawal symptoms (DT and seizures).

Methods

Patients

The patient registries of the last 10 years (1995–2005) from two hospitals in central Switzerland (Kantonsspital Luzern, Kantonales Spital Wolhusen) were screened for patients who had been discharged with an ICD diagnosis of DT (F10.4) or alcohol withdrawal seizures (F10.3). Only patients on whom a 12-lead-electrocardiogram (ECG) was recorded on the day they developed DT or seizures were included in the study. For patients who were admitted with DT or seizures this was the ECG written at the time of admission. For patients who developed DT while being hospitalised the ECG written on the day the DT was diagnosed was analysed. 13 patients with DT did not fulfil these criteria and were not included in the study.

Data collected

Because many drugs can induce ECG changes, all drugs taken before admission were recorded and compared with an online list (www.qt drugs.com) from the University of Arizona.

Information was also extracted from the following documented investigations:

Electrocardiographic recordings: Electrocardiographic lead placement was according to standard positions. Tachycardia was defined as heart rate >100/minute and bradycardia as heart rate <60/minute. The following intervals were measured in lead II: PQ, QRS, QT.

QT interval: The corrected QT interval (QTc) was obtained using Bazett's formula, in which the QT interval

is adjusted for heart rate by dividing it by the square root of the QT interval [17]. A long QT interval was defined as QTc >440 milliseconds (ms) for males and QTc >460 ms for females [18]. If the clinical situation required more than one ECG recording on the day the diagnosis of DT or seizures was made, then the longer QTc interval was taken for analysis.

Blood count and chemistry: Values for leukocyte count, haemoglobin, mean corpuscular volume (MCV) of the erythrocytes, platelet count, plasma concentration of sodium and potassium were collected. A leucocyte count of $4-10 \times 10^9/l$, haemoglobin values of 140–160 g/l in males, 120–160 g/l in females, a thrombocyte count between of between $150-450 \times 10^9/l$, a middle corpuscular volume (MCV) of 83–99 femtoliter (fl), serum sodium concentrations of 136–145 mmol/l, and serum potassium concentration of 3.5–5.1 mmol/l were considered as normal.

Body temperature: Fever was defined as auricular temperature >37.5 °C, hypothermia as a temperature <36.0 °C.

Cerebral imaging: In 19 patients a computed tomography or magnet resonance imaging was performed to exclude or document cerebral atrophy, acute bleeding or ischaemia, infection or neoplasia.

Statistical analysis

Results are summarised by their mean and standard deviation (SD). For statistical analysis STATVIEW software from the SAS Institute (www.sas.com) was used.

Results

Patient characteristics

A total of 49 patients, 38 males and 11 females, with a mean age of 48 (10.4) years were included in the study. 23 patients (49%) were admitted to the hospital with DT and 16 (34%) with convulsions. The remaining 10 patients (17%) developed DT while being hospitalised for another reason (alcoholic hepatitis, pancreatitis, pneumonia, cerebral bleeding). 41 patients (84%) were not on any

medication upon admission, 5 (10%) were on neuroleptics, 2 (4%) on benzodiazepines and 1 (2%) on opioids.

19 patients (39%) underwent cerebral imaging (33% computed tomography, 6% MRI), of whom 14 (74%) had cerebral atrophy. One patient had an acute cerebral bleeding.

The laboratory characteristics on admission are summarised in table 1.

Table 1
Laboratory characteristics on admission.

Laboratory parameter	Mean (SD)	Range	Normal Range	Below normal	Above normal
Sodium	135.3 (6.1)	98–176 mmol/l	136–145 mmol/l	41%	2%
Potassium	3.7 (0.5)	2.5–5.3 mmol/l	3.5–5.1 mmol/l	35%	2%
Leucocytes	8.0 (3.2)	$2.6-17.0 \times 10^9/l$	$4-10 \times 10^9/l$	8%	25%
Haemoglobin	137.7 (16.8)	98–176 g/l	140–160 g/l (m) 120–160 g/l (f)	49%	12%
Thrombocytes	139.2 (91.6)	$33-538 \times 10^9/l$	$150-450 \times 10^9/l$	65%	2%
MCV	98.1 (7.1)	81–110 fl	83–99 fl	0%	55%

Table 2

Comparison of clinical and laboratory parameters between subjects with normal and prolonged QTc values.

	QTc normal (n = 18) Mean (standard deviation)	QTc prolonged (n = 31) Mean (standard deviation)
Age (years)	43.8 (7.7)	51.3 (10.7)
Sodium mmol/l	135.4 (6.8)	135.2 (5.7)
Potassium mmol/l	3.7 (0.6)	3.7 (0.5)
Kreatinin $\mu\text{mol/l}$	69.0 (26.1)	86.4 (59.1)
Temperature C	37.7 (1.0)	37.5 (0.5)
Hospital stay in days	13.3 (6.9)	14.1 (9.6)
Neuroleptics use	n = 3 (60%)	n = 2 (40%)
Delirium tremens	n = 13 (39%)	n = 20 (61%)
Withdrawal seizures	n = 5 (29%)	n = 11 (71%)

ECG analysis and correlation with clinical and laboratory values

Evaluation of rhythm analysis on admission revealed that the majority of the patients (55%) were in normocardic sinus rhythm. 35% had tachycardic sinus rhythm, 6% bradycardic sinus rhythm and 4% had supraventricular tachycardia. The analysis of the baseline ECG's revealed 5 (10%) chronic infarctions, 1 (2%) bundle branch block, 2 (4%) ST-segment elevations and 1 (2%) left ventricular hypertrophy. The ECG intervals (PQ, QRS, QT, QTc) are summarised in box plots

in figure 1. The mean duration of the different intervals (with SD) were: PQ 160 ms (42), QRS 90 ms (21), QT 360 ms (42), QTc 458 ms (42).

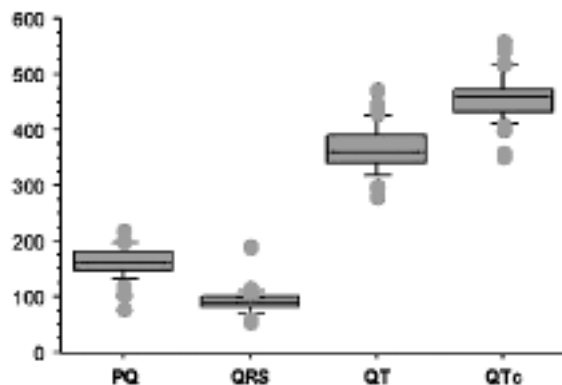
18 patients (37%) had a normal QTc interval (<440 ms in males, <460 ms in females) and 31 patients (63%) had a prolonged interval. Approximately 60% of the patients with DT and 70% of the patients with seizures had a prolonged QTc. 8 patients (16%) had a markedly prolonged QTc (>500 ms). For the laboratory values there were no major differences between the group with a prolonged QTc and the group with a normal QTc (comparable sodium, potassium and creatinine values, table 2). The prevalence of a prolonged QTc was also comparable between males and females in the study population (60% in females and 64% in males). However, patients with a prolonged QTc were older than patients with normal QTc (43.8 vs 51.3 years, figure 2). The average hospital stay was 13.8 days and this was comparable between subjects with a normal and prolonged QTc (table 2).

Five patients (10%) were on neuroleptics, which potentially prolong the QTc interval. Two of these patients had a prolonged QTc interval (QTc 460 and 445 ms) but neither developed an arrhythmia. Five patients (10%) developed arrhythmias following admission. Three of these patients developed ventricular tachyarrhythmias; two torsades de pointes (figure 3) and one sustained ventricular tachycardia.

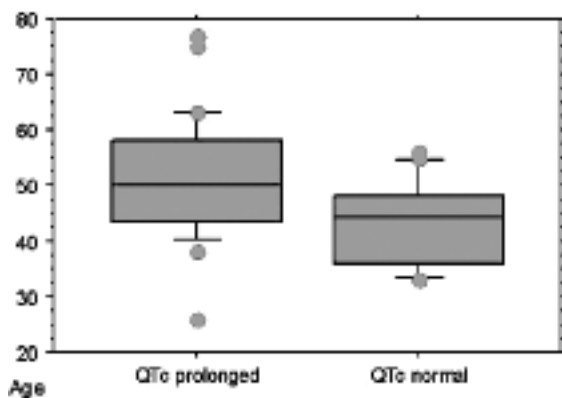
The two patients who developed torsades de pointes were 45 (Patient 1) and 55 (Patient 2) years old. Both had been admitted because of DT and developed the arrhythmia 1 and 2 days, respectively, after admission. The QTc durations before the torsades were markedly prolonged (520 and 525 milliseconds, respectively). Neither of these patients had had a pretreatment with a reported QT-prolonging drug. Both received an alpha-blocking agent, clonidine, and lorazepam (a benzodiazepine) after admission. Patient 1 had slight hyponatraemia (133 mmol/l) and normal potassium and calcium values. Patient 2 had a slight hypokalaemia (3.2 mmol/l) and normal sodium and calcium values. Cerebral imaging with a computer tomography showed cerebral atrophy in both patients but no signs of acute bleeding or ischaemia. Both patients underwent transthoracic echocardiography. Patient 1 had diffuse hypokinesia and a

Figure 1

Box plots of the duration (ms) of various ECG intervals.

**Figure 2**

Box plots of the age in patients with a prolonged (n = 31) and normal (n = 18) QTc.

**Figure 3**

Torsade de pointes in a patient with delirium tremens.



reduced left ventricular ejection fraction of 40%. No left ventricular hypertrophy or pulmonary arterial hypertension was noted. Patient 2 had a normal left- and right ventricular function with signs of slight left ventricular hypertrophy.

There were no deaths during the hospital stay and all 49 patients were discharged in a normocardic sinus rhythm.

Discussion

This study provides evidence that ECG abnormalities are significant in severe alcohol withdrawal syndromes. A long QTc was present in 31 out of 49 patients during alcohol withdrawal. Three patients developed life-threatening ventricular tachyarrhythmias; two had torsade de pointes and one a sustained ventricular tachycardia. Our results confirm the previously reported high incidence of long QTc intervals during alcohol withdrawal syndrome [13]. However, while that study found the QTc interval prolongation (>440 ms) in 47% of the patients, we found QTc prolongation in 63% of the patients. These studies are both retrospective and the patient numbers too small to make a precise statement about the prevalence of QT prolongation in alcohol withdrawal. However, we assume that the higher incidence in our study might be due that only patients with severe alcohol withdrawal symptoms were included.

The long QT syndrome is a disorder of cardiac repolarisation [19] and is associated with an increased risk of torsade de pointes [20, 21]. The long QT syndrome may be genetic or acquired [22]. Acquired long QT syndrome usually results from drug therapy, electrolyte disturbances, impaired hepatic and/or renal function, underlying heart disease and bradycardia. On admission, five patients were on drugs that potentially can prolong the QT interval. The QTc was prolonged in two of these patients but neither had any of the dangerous arrhythmias mentioned above. 35% of the analysed patients had hypokalaemia but there were no major differences between the patients with a prolonged QT interval and those with a normal QT interval. Hypomagnesaemia, a known phenomenon in alcoholic patients [23, 24], was not measured.

Central nervous system disorders are known to be responsible for the onset of cardiac alterations frequently observed in the ECG [25–27], particularly a prolongation of the QT interval [28]. The majority of studies suggest that the ECG abnormalities are a consequence of the disturbances in the autonomous system, due to neurologic disease, promoting a local excess of catecholamines. Although the causes of cardiac alterations are a matter of scientific speculation, evidence exists that myocardial lesion is mediated by catecholamines, and an important left ventricular dys-

function with the liberation of cardiac proteins such as Troponin I occurs in some cases [29]. Since we did not find a high proportion of electrolyte disturbances or intake of QT prolonging drugs, central nervous stress possibly explains the large proportion of patients with a prolonged QT interval in our study.

Both this and the previous [13] study were retrospective but an important elevated risk of sudden death for patients with intensive symptoms during alcohol withdrawal is clearly indicated. The two patients who developed torsade de pointes had both a markedly prolonged QTc (520 and 525 ms) on admission. One might assume that patients with a QTc >500 ms are at an increased risk of developing cardiac arrhythmias. Because only a small part of our patients (n = 5) were on neuroleptics we are not able to make a precise statement regarding the influence of QTc prolonging drugs on the risk for cardiac arrhythmias.

The present results indicate that patients presenting with DT or alcohol withdrawal seizures should undergo ECG screening and manual measurement of the QTc interval. Additionally neuroleptic agents, which despite the repeatedly reported concern of increased risk for torsade de pointes [30] are still recommended for severe agitation in alcohol withdrawal syndromes [15], should be assessed. QTc prolongation following cerebral stress and treatment with QT prolonging drugs might be a dangerous combination.

Considering the lack of data there is undoubtedly a need for a larger prospective study.

Despite the fact that the in-hospital mortality in our study was 0%, we recommend that patients with heavy alcohol withdrawal syndromes, especially those with a markedly prolonged QTc (>500 ms) or those on QT prolonging drugs should be monitored in an intensive or intermediate care unit to guarantee adequate therapy for ventricular tachycardias.

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