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# Hypokalemia is associated with lengthening of QT interval in psychiatric patients on admission

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ABSTRACT

Several studies have revealed a relatively high frequency of hypokalemia in the general psychiatric population. This may be explained by adrenergic stimulation observed in the acute phase of psychiatric disorders. Little is known about the effects of hypokalemia on cardiac repolarisation in these circumstances. The current study was designed to determine if the hypokalemia observed among patients with acute psychiatric disorders can cause significant QT interval prolongation, and thus increase the risk of ventricular arrhythmia. Electrocardiograms were obtained in 282 non-selected patients admitted to a psychiatric unit. Heart-rate adjusted QT intervals (QTc) were compared to serum potassium levels and to other risk factors for QT prolongation (bradycardia, age, gender, and administration of antipsychotics). Hypokalemia, diagnosed in more than 11% of the patients, was associated with a significantly longer QTc interval (means $423.5 \pm 40$ ms vs $408.5 \pm 31$ ms), as was female sex. Multiple linear regression analysis on the studied risk factors revealed that only hypokalemia and female sex were independently associated with lengthening of the QT interval. According to our results, hypokalemia seems to be one of the most important risk factors for QT prolongation. We therefore strongly recommend that psychiatric patients should be screened for hypokalemia on admission.



## 1. Introduction

Since the early 1960s, sudden deaths have been observed in patients receiving psychotropic drugs (Haddad and Anderson, 2002) and it has been reported that the administration of antipsychotics may trigger QT interval prolongation (Witchel et al., 2003). This abnormality, which represents a prolonged duration of individual action potentials in cardiac myocytes, can degenerate into torsade de pointes (TdP), a polymorphic ventricular tachycardia that can progress to ventricular fibrillation and sudden death (Glassman and Bigger, 2001; Haddad and Anderson, 2002; Gowda et al., 2004). But are antipsychotics the only risk factor at play? This article looks into other risk factors and their relative importance.

The risk factors for QT prolongation reported to date include the following: congenitally long QT syndromes, female gender, old age, bradycardia, heart disease, and electrolyte imbalance (De Ponti et al., 2002; Haddad and Anderson, 2002; Gowda et al., 2004). It would seem that the presence of one or more risk factors is required to precipitate ventricular arrhythmia in a patient with iatrogenic QT prolongation (Haddad and Anderson, 2002). TdP and sudden death are most likely to occur when antipsychotic drugs are associated simultaneously with other risk factors known to cause QT prolongation. Our study was designed to understand their relative importance, in particular for hypokalemia, which is known to reduce the repolarizing current iKr (Facchini et al., 2006) and seems to occur frequently in the general psychiatric population (Kemperman et al., 1988; Hatta et al., 1998).

The pathogenesis of hypokalemia in psychiatric patients has not yet been fully investigated and little is known about its effects on cardiac repolarization in these circumstances. Is there a causal association between hypokalemia and the risk of developing ventricular arrhythmia when patients present acute psychiatric disorders? Might this factor be linked to the high incidence of sudden death observed among patients receiving antipsychotic medication?

The aims of this study were:

1) to determine the occurrence and causes of hypokalemia in psychiatric patients on admission.
2) to evaluate the influence of hypokalemia on cardiac repolarization at the time of patients' admission, and compare this with the following risk factors for QT prolongation: bradycardia, old age, gender, and the administration of antipsychotic drugs.

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## 2. Methods

### 2.1. Subjects

The study was carried out during a 16-month period (July 2002 to October 2003) among patients hospitalised on a psychiatric unit in northeastern France. All admitted subjects were enrolled in the study. Patients who had multiple admissions during the study period were included only at the first admission. Patients with acute alcohol, drug intoxication, or physical medical disorder were included after initial admission for medical treatment.

The protocol did not interfere with usual treatments, and surveillance (ionograms and electrocardiograms) was consistent with standard clinical practice in France. The data were anonymously recorded after informed written consent had been obtained.

### 2.2. Biochemical measurements and QT interval measurement

On the day of admission, a 12-lead electrocardiogram (MAC 1200 ST, GE Medical Systems, Milwaukee, WI, USA) with a paper speed of 25 mm/s was performed before initial treatment when possible. The QT interval was measured manually (QTm) from the onset of the QRS complex to the end of the T wave and, in order to limit the influence of heart rate on the QT interval, the measurement was corrected (QTc) by Bazett's formula defined by $QTc = QTm/\sqrt{RR}$ (Bazett, 1920).

Blood samples were obtained from the patients at the same time as the ECG, and levels of potassium were measured. In cases where hypokalemia was diagnosed (range: 3.5 to 5.0 mmol/l), the authors investigated the cause and corrected it.

### 2.3. Statistical method

As other factors might have affected the QT interval, in addition to analyzing the QT interval with regard to serum potassium levels, the impact of other variables was investigated. The major risk factors for QT prolongation included in the analysis were bradycardia under 55 beats/min, age over 65 years, female sex, and the administration of antipsychotics (Reilly et al., 2000; Viskin et al., 2003).

In order to identify the effects of hypokalemia and the other variables on the QTc interval, we first performed a univariate analysis using the Mann–Whitney *U*-test. For the analysis, patients were divided into different groups according to serum potassium levels and the presence or absence of the risk factors for QT prolongation.

In the second part of the analysis, the variables associated with QT lengthening in the univariate analysis were included in a multiple logistic regression analysis, to identify independent risk factors for QT prolongation.

A *P* value of less than 0.05 was considered statistically significant for all tests. Data are expressed as means ± SD, and as medians and interquartile ranges. All analyses were performed using version 8.0 of Stata™ software.

## 3. Results

### 3.1. Clinical and biochemical data

A total of 330 patients, aged18–92 years, were enrolled during the study period. However, analyses were performed on only 282 patients (101 [36%] men, 181 [64%] women; mean age 43 years, range 18–92) for whom the ionograms and electrocardiograms were usable. As mentioned above, no patients presented acute decompensated heart failure. One hundred [35%] patients were taking antipsychotics.

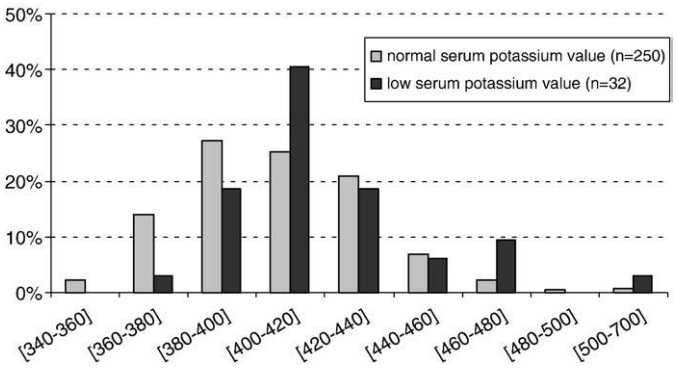


**Fig. 1.** Difference in QTc interval distribution according to serum potassium values.

**Table 1**
Univariate analysis according to hypokalemia and low normal potassium levels.

| Potassium level | QTc (mean) | *P* |
|---|---|---|
| <3.5 mmol/l (*n* = 32) | 423.5 ± 40 ms | 0.0045* |
| 3.5–4 mmol/l (*n* = 145) | 413 ± 36 ms | |
| >4 mmol/l (*n* = 105) | 403 ± 23 ms | |

Values expressed as means measured in milliseconds.

Twelve patients presented bradycardia [range 48–54 beats/min] without signs or symptoms of hemodynamic instability.

The proportion of patients with hypokalemia seemed unexpectedly high, at 11.35% (32 patients). The low potassium values ranged from 2.7 mmol/l to 3.4 mmol/l (ranges, 3.5 to 5.0 mmol/l). All of the patients with hypokalemia rapidly revealed a tendency towards normalisation of serum potassium levels within 1 or 2 days.

Among patients presenting with hypokalemia, we assessed whether the diagnosed electrolyte disturbances had any obvious aetiology. Of the seven patients hospitalised after admission to medical units for overdosing, only two had taken drugs that could induce hypokalemia: bisacodyl (laxative) and indapamide (thiazidic diuretic). But as mentioned above, these patients were not enrolled during the acute phase of their intoxication. For the other patients, no treatment could explain a low concentration of serum potassium. Four out of 32 in the hypokalemia group were hospitalised for alcohol withdrawal, one of whom had concomitant moderate diarrhoea.

### 3.2. Correlation between serum potassium level and QTc interval

Univariate analysis demonstrated that there was a significant relationship between hypokalemia and lengthening of the QTc interval (means 423.5 ± 40 ms vs 408.5 ± 31 ms, $p = 0.0289$). We found a significant inverse correlation between serum potassium levels and QTc interval ($p = 0.005$). So, we also studied the effects of low normal potassium levels (3.5–4 mmol/l) on cardiac repolarisation. According to our results, both hypokalemia and low normal potassium levels were significantly associated with lengthening of the QTc interval [Fig. 1, Table 1].

### 3.3. Effects of risk factors for QT prolongation on the QTc interval

Univariate analysis demonstrated that there were significant relationships between QTc lengthening and hypokalemia, female sex, age over 65 years and the administration of antipsychotics [Table 2]. Bradycardia was found to have no significant impact on the QTc interval.

A multivariate analysis was performed using multiple linear regression with covariates chosen on the basis of the univariate

**Table 2**
Univariate analysis of risk factors for QTc prolongation (Mann–Whitney *U*-test).

| Variables | Present | Absent | *P* |
|---|---|---|---|
| Potassium values<3.5 mmol/l | 414.5 [403–436.5] (*n* = 32) | 406 [388–425] (*n* = 250) | 0.0289* |
| Bradycardia<55 beats/min | 388.5 [377.5–408.5] (*n* = 12) | 408.5 [390–426] (*n* = 270) | 0.0590 |
| Age>65 | 424 [402–441] (*n* = 25) | 406 [388–425] (*n* = 257) | 0.0141* |
| Female sex | 413 [394–428] (*n* = 181) | 399 [383–419] (*n* = 101) | 0.0012* |
| Antipsychotics | 411 [391–426] (*n* = 100) | 407 [388–426] (*n* = 182) | 0.0001* |

Values expressed as median QTc measured in milliseconds [interquartile range].