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KCNH2 polymorphism and methadone dosage interact to enhance QT duration

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ABSTRACT

Background: Many drugs increase the duration of the QT interval of patients, potentially leading to harmful effects such as polymorphic ventricular arrhythmias. Most of these drugs do so by inhibiting the rapid component IKr of the delayed rectifier potassium current IK. Methadone is the most prescribed heroin maintenance treatment and is known to inhibit the cardiac potassium channel hERG, which recapitulates IKr. In order to evaluate if any polymorphism of potassium channels' genes could explain some of the "idiosyncratic" QT prolongations observed in patients treated with methadone, we tested the association between *KCNE1*, *KCNE2*, and *KCNH2* polymorphism and the QT interval prolongation in those patients, controlling for other variables associated with a decrease of the repolarizing reserve.
Methods: A cohort of 82 patients treated with stable dosage of methadone (mean dosage 65 mg/d) for at least three months was genotyped for five polymorphisms in *KCNE1*, *KCNE2* and *KCNH2* genes and had their corrected QT (QTc) assessed.
Results: The mean QTc interval was 415 ± 34 ms. In a linear regression model, longer QTc interval was associated with methadone dosage and with one genetic factor. Each copy of a Lys allele at codon 897 of *KCNH2*, the gene that encodes the cardiac potassium voltage-gated channel hERG, was associated with a 15.4 ms longer QTc (95% CI [4.6–26.2]; $p = 0.001$).
Conclusion: KCNH2 genotyping may be relevant in the analysis of cumulative risk factors for QT prolongation in patients on methadone maintenance treatment.
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1. Introduction

The synthetic mu-opioid receptor agonist methadone has been used for more than 40 years as a maintenance treatment for heroin dependence. The mix of the two enantiomers, (S)- and (R)- is currently used in as much as 75% of the 700,000 opioid-dependent patients on maintenance treatment in Europe (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2012). Cost-effective studies have evidenced that methadone was less expensive and more efficient than buprenorphine (Connock et al., 2007; Doran et al., 2003). In opiate-dependant individuals, methadone decreases mortality rates by reducing the number of fatal heroin overdoses, decreases HIV seroconversion rates, increases adherence to treatment programs and improves patients' social and general functioning (Kleber, 2008).

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Apart from the risk of fatal overdose during treatment onset, one of the major adverse effects of methadone treatment is the occurrence of QT lengthening that may lead to potentially lethal ventricular arrhythmia such as Torsades de Pointes (TdP) and sudden death. Although this is particularly true in patients taking high doses of methadone, abusing other drugs (especially cocaine and alcohol) or also taking cardiotoxic drugs (Butler et al., 2011; De Bels et al., 2003; Gil et al., 2003; Krantz et al., 2002; Lipski et al., 1973), some factors decreasing the patient's cardiac "repolarisation reserve" may facilitate such an effect. Indeed, even if imperfect, the duration of the QT interval on a surface electrocardiogram (ECG) is a fair surrogate for the underlying cardiac mechanisms causing arrhythmias.

Prospective studies have demonstrated that methadone can induce QT prolongation (Ehret et al., 2006; Martell et al., 2005; Roy et al., 2012; Wedam et al., 2007). However, not all patients on high doses of methadone have a prolonged QT, and when it is the case, the QT prolongation induced by chronic methadone varies considerably between patients, suggesting the implication of specific individual risk factors. Usual factors specifically associated with methadone-induced QT lengthening include heart and liver disease, electrolyte abnormalities, concomitant use of another QT-prolonging drug or CYP3A4 inhibitors that increase the plasma concentrations of the latters, and a daily oral methadone dose of more than 100 mg (Mayet et al., 2011). Nevertheless, major QT prolongation and arrhythmia may occur in the absence of identified risk factors suggesting that other factors are implicated.

Cardiac ventricular repolarization is influenced by factors such as heart rate, electrolyte disturbances, age, gender and medication susceptible to block potassium channels. Heritability studies have suggested that genetic factors are also involved in the control of cardiac repolarization (Dalageorgou et al., 2008). Indeed, mutations in the genes encoding the cardiac potassium ion channels have been shown to be responsible for congenital QT lengthening and familial ventricular arrhythmia disorders associated with a high risk of sudden death. These familial diseases include the long QT syndromes (LQTS), the most frequent of the so-called "channelopathies" (Brugada et al., 2004; Judson et al., 2006; Maremmani et al., 2005; Sanguinetti and Mitcheson, 2005). Congenital Long QT syndrome has been evidenced to be a risk factor for detrimental QT prolongation in individuals on methadone (Anchersen et al., 2010), but single nucleotide polymorphisms (SNPs) in genes encoding cardiac potassium voltage-gated channels (*KCNE1*, *KCNE2*, *KCNH2*) have been so far only associated with modifications in the QT of healthy individuals (Gouas et al., 2005, 2007; Marjamaa et al., 2009), families of patients with long QT syndrome (Gouas et al., 2007) and with some rare cases of drug-induced torsades (Abbott et al., 1999). Methadone blocks the cardiac ionic channels hERG, the human *ether-a-Go-Go* tetrameric channel encoded by *KCNH2* and responsible for the IKr current, in a concentration-dependent manner (Katchman et al., 2002). We therefore aimed to evaluate whether some SNPs could be a risk factor during methadone treatment in a cohort of patients on methadone maintenance. We particularly examined the association between corrected QT (QTc) duration and polymorphism of *KCNE1*, *KCNE2*, and *KCNH2* genes encoding cardiac potassium voltage-gated channels that are involved in the repolarization process.

2. Materials and methods

2.1. Study design and patients

All patients met the criteria for opioid dependence according to the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) and were at stable dosage of methadone maintenance treatment for more than 3 months, and responders according to our definition: no current illicit opioid dependence criteria, no current cocaine, alcohol or benzodiazepine dependence criteria, although drug use could be present. Written informed consent was obtained from each subject after they had received a complete description of the study and been given the chance to discuss any questions or issues. The study was approved by the Ethics Committee of Paris, Ile-de-France (CPP VI) and was registered to the clinicaltrials.gov website (NCT00894452).

All patients had four Caucasian grandparents to avoid any bias attributable to inter-ethnic variation. Demographic and clinical informations, including illicit drug use and currently prescribed drugs, were collected during a clinical interview. Laboratory data included HIV and HCV serologies.

2.2. QT measurement

Patients underwent resting ECG recording with a standard 12-lead digital recording apparatus. The QT measurements of all patients were made under steady state methadone conditions. Patients were at the same methadone dosage for at least three months, ECG recording was made before the morning methadone intake. None of the patients had a history of known prolonged QT, TdP or syncope at inclusion.

QTc was calculated with Bazett's formula. ECGs were blindly read by two trained senior cardiologists. The QTc interval was considered "borderline" if it exceeded 430 ms for men and 450 ms for women, and was considered to be "prolonged" if superior to 450 ms (men) or 470 ms (women) (Al-Khatib et al., 2003; Goldenberg and Moss, 2008).

All patients with an abnormal QTc were individually followed-up by a senior cardiologist, particularly those with a QTc of more than 500 ms, who were considered to have a clinically significant risk of developing arrhythmia and TdP.

2.3. Genotyping

Blood was collected by venipuncture for genetic analysis. DNA was extracted from blood cells with a Promega Maxwell 16 extractor, as recommended by the manufacturer (Promega France, Charbonnières-les-Bains, France). All patients were genotyped for polymorphisms of potassium cardiac channel genes (*KCNH2* NG_008916.1: g.34481 A>C, p.Lys897Thr -rs1805123; *KCNE2* A>G, p.Thr8Ala -rs2234916-; and *KCNE1* G>A, p.Asp85Asn -rs1805128-; G>A, p.Ser38Gly -rs1805127-; -50-129T>C -rs2236609-), on Illumina microarrays (Repac DNA Microarrays), as recommended by the manufacturers. Hybridizations were performed by Integragen (Evry, France). The resulting signals were validated and analyzed with custom-written software (Pharcra). Reports were generated with three different genotypes per SNP. Genotypes were confirmed by real-time PCR (StepOne Plus, Applied Biosystems) with predesigned kits (Applied Biosystems).

2.4. Statistical analysis

Clinical data are presented as means ± standard deviation, median and range or numbers, percentages, as appropriate. For genetic data, the absence of deviation from Hardy–Weinberg equilibrium was checked for each SNP by a Chi-square test with one degree of freedom. Allelic frequencies confidence intervals were obtained from bootstrap. Relation between clinical and genetic variables of interest and the QTc interval were first explored through non-parametric univariate analysis (Spearman's rank correlation for continuous variables, Kruskal–Wallis test for categorical variables). Variables that were significantly associated with QTc in the univariate analysis or that were known to influence QTc length in methadone-treated patients or cardiac ventricular repolarization were included in an ascendant stepwise regression model (level for entry $p < 0.10$). The p-values were obtained with permutation tests in case of departure from normality). All statistical analyses were performed with R software version 3.0.2, Vienna, Austria, and additional packages lmPerm (for permutation tests) and SARP (written by EC).

3. Results

3.1. Patients and QTc interval

The cohort comprised 82 Caucasian patients aged between 23 and 67 years old (mean: 42 years); 60 (73%) were men. The average QTc under treatment was 415 ± 34 ms (mean ± standard deviation; range: 350–575 ms). Sixteen patients (20% of the cohort) had abnormal QTc interval, all males: 8 border-line (>430 ms) and 8 prolonged (>450 ms). Two patients had a QTc of 500 ms and above, one had a QTc of 499 ms. During the prospective two years follow–up, one of these two patients, who was receiving 120 mg per day of methadone and an antipsychotic treatment with chlorpromazine, died of unknown causes at home. A benzodiazepine intoxication was suspected, because he had two previous episodes of massive "recreational" benzodiazepine intake, but an arrhythmia cannot be ruled out. The second patient who had been stable for several years with a methadone dosage of 20 mg per day started a slow tapering of the medication. At the last visit he was receiving 4 mg per day

Table 1
Association of demographic and clinical variables with QTc interval.

Variable	Value	QTc	*p* Value
Methadone dose (mg per day)	57 [10–320]		0.0891
Taking at least one other medication			
Yes	53 (65)	416 [350–575]	0.597
No	27 (35)	409 [358–499]	
Among which taking at least one drug associated with QT prolongation[a]			
Yes	20 (24)	411 [402–421]	0.301
No	62 (66)	410 [358–499]	
Current cocaine use			
Yes	34 (41)	412 [358–512]	0.516
No	48 (59)	412 [350–575]	
Current alcohol use			
Yes	46 (56)	418 [398–575]	0.796
No	31 (44)	406 [350–512]	

QTc are given as median [range]. Values for categorical variables are given as number of cases (percentage). Test statistic is the Spearman rank's correlation coefficient for methadone dose and difference between the two groups for categorical variables. *P*-values are for non-parametric tests.

[a] According to the classification of ArizonaCERT (http://www.torsades.org accessed May 1st 2013). Among those 20 patients, 11 were under antipsychotic treatment and 9 antidepressant and 5 had both.

and still had a prolonged QTc of 480 ms. The third one, whose QTc was of verified twice at 499 ms, with no concurrent medication and a methadone dosage of 40 mg per day was lost to follow up.

3.2. Genotypes of cardiac sodium and potassium voltage-gated channel genes

Two SNPs were monomorphic: KCNE1 rs1805128 p.Asp85Asn (the 82 patients were GG) and KCNE2 rs22349916 Thr8Ala (the 82 patients were AA). Hence, they were not further considered in the analysis. All remaining SNPs were in Hardy-Weinberg equilibrium ($p = 0.83$ for rs1805123, $p = 0.48$ for rs1805127 and $p = 0.26$ for rs2236609, Chi-square test with 1 degree of freedom).

For SNP rs1805123, with a lysine (Lys) or a threonine (Thr) codon in position 897 of *KCNH2*, the allelic frequencies were 0.659 (95% CI: [0.585, 0.731]) for A (897Lys) and 0.341 ([0.269, 0.415]) for C (897Thr). The 897Lys hence seemed to be slightly less represented than in the European HapMap control population ($n = 113$, $f = 0.761$, $p = 0.0362$, Fisher's exact test).

Univariate analysis results are given in Table 1. Among polymorphism, only rs1805123 (*KCNH2*), was significantly associated with QTc duration ($p = 0.001$), either considered in a co-dominant approach (number of Lys alleles), where each copy was associated with a +15.4 ms [4.6–26.1] longer QTc, or a dominant-recessive approach (see Table 2). For instance, with the dominant-recessive model (AA+AC) versus CC, (AA+AC) mean QTc was 419 ± 34 (AA+AC, $n = 72$) versus 383 ± 19 ms (CC, $n = 10$), $p = 0.0004$ (Kruskal–Wallis test), thus leading to a mean 13.24 ms [1.9–28.4] longer QTc. All the 16 patients (20%) with border-line or prolonged QTc value carried at least one *KCNH2* 897Lys allele. Proportion of patients presenting abnormal QTc was slightly higher in homozygote AA patients (27.8%) than in the heterozygous patients (16.7%). Globally, odds of abnormal QTc increase with increasing number of Lys alleles (OR: 2.65 [1.07, 7.72]; $p = 0.034$, logistic regression). Among other variables, only methadone dose was significantly associated with QTc interval. However, when considered alone, dose was not associated with abnormal QTc (OR: 1.00 [0.99, 1.01], $p = 0.45$, logistic regression).

The step-up multivariate regression, and all other multivariate model tests, lead to only these two variables as significant predictors of QTc interval in our population: methadone daily dose ($p = 0.027$) and *KCNH2* rs1805123 number of 897Lys (0, 1 or 2; $p = 0.001$).

Last, patients of the Lys897Thr genotypes did not differ for any other variable, except that Thr/Thr patients where slightly younger than other patients (36 versus 42 years old, $p = 0.0382$, Mann–Whitney test). However, adding age in the previous model did not explained better QTc duration.

4. Discussion

Methadone is a life-saving treatment for heroin addiction. Nevertheless, sudden deaths and severe cardiac arrhythmias in treated patients have also been reported (Krantz et al., 2002). QTc lengthening is a side effect that occurs with high between-patient variability among methadone maintained patients (Maremmani et al., 2005; Roy et al., 2012). This is the first evidence for an association between QTc interval and a polymorphism in a gene encoding for a cardiac voltage gated channel that suggests a cumulative effect of methadone dosage and this polymorphism on QTc.

The main limitations of this study were that QTc interval was not prospectively evaluated and that the characteristics of French patients under methadone treatment may not be generalized to other countries, especially because French patients receive on average lower doses than in other countries. Furthermore, the distribution of the predisposing allele of this polymorphism was slightly less frequent in our sample to that in other Caucasian sample described (HapMap). This allele, A (897Lys), is the most frequently observed in Caucasians (0.761; HapMapCEU), Africans (0.983; HapMap-YRI) and Asians (0.977; HapMap-HCb and JPT).

The role of methadone dosage on QTc prolongation remains controversial. The mean daily dose in our patient population was 65 mg/day, the median 57 mg/day, which is within the range of daily doses usually prescribed in France. In this study, an abnormal or prolonged QTc was observed in 20% of the patients. Some authors found that between 17% and 30% of patients on doses above 100 mg/day had a prolonged QTc (Mayet et al., 2011). On the other hand, Roy et al. found no evidence of a dose–response relationship in patients treated with low doses of methadone (mean of 80 mg/day; Roy et al., 2012).

Table 2
Association between genotypes for polymorphisms in genes encoding cardiac ion channels and QTc interval.

Gene	SNP alleles (A/a)	Genotypes	*N* (%)	QTc median [range]	*p* Value
KCNH2	rs1805123	AA	36 (44)	420 [366–375]	0.001
	p.Lys897Thr	AC	36 (44)	413 [365–512]	
		CC	10 (12)	385 [350–409]	
KCNE1	rs1805127	AA	14 (17)	408 [369–462]	0.747
	p.Ser38Gly	GA	36 (44)	416 [358–512]	
		GG	32 (39)	408 [350–575]	
KCNE1	rs2236609	AA	17 (21)	412 [369–462]	0.847
	-50–129 T/C	GA	35 (43)	415 [358–512]	
		GG	30 (37)	408 [350–575]	

P-values are for Kruskal–Wallis test.

The interaction between methadone dosage and genetic factors could be an explanation for these apparent discrepencies. Another explanation could be that in other studies, methadone dosage are in a narrow range, hence reducing the power to detect a dose–effect relationship.

Based on a rationale biological basis, we choose to investigate the role of five polymorphisms related to three genes (*KCNE1*, *KCNE2*, and *KCNH2*) encoding proteins involved in the cardiac repolarization process, especially the IKr rapid component of the potassium voltage channel. All of those genes have been previously implicated in long QT syndromes (Krantz et al., 2002) and influence channel function *in vitro* (Judson et al., 2006; Tester et al., 2006).

KCNH2 encodes the hERG potassium channel. According to Krantz et al. (2005) almost all the drugs implicated in drug-induced Long QT bind hERG. The Lys897Thr polymorphism has been shown to influence hERG function *in vitro*, as the minor allele 897Thr is associated with activation of the hERG channel at more negative potentials and faster cardiac repolarization (Bezzina et al., 2003). Furthermore, methadone blocks hERG in a concentration-dependent manner (Katchman et al., 2002).

The *KCNH2* polymorphism at codon 897 has little effect on QTc in healthy individuals. A Finnish study on more than 5000 healthy subjects found that the 897Lys allele was associated with a mean QTc interval prolongation of 2.6 ms (Marjamaa et al., 2009). Another study, by Newton-Cheh et al. (2007), on 1730 subjects from the Framingham cohort, found that the QTc interval of individuals carrying at least one Lys897 allele was 3.9 ms longer than that of Thr homozygotes after adjustment for age, sex and RR interval on ECG. In this first study of methadone maintained patients, we found a mean prolongation of QTc of 14 ms (95% confidence interval: 3–24 ms) per 897Lys allele of *KCNH2*, which can be relevant in the analysis of cumulative risk factors. We found a statistical association but cannot conclude from our data that "A" allele is associated with QT prolongation or that "C" allele is protective against QT prolongation during methadone maintenance treatment.

Moreover, the amino acid encoded by codon 897 of *KCNH2* is located within the cytoplasmic C-terminal domain of hERG. Gustina et al. recently evidenced that the N- and C-terminal domains of the hERG subunits interact within the tetrameric channel, regulating its deactivation gating (Gustina and Trudeau, 2011).

In conclusion, we found that 20% of the patients in a French cohort of patients with relatively low doses of methadone maintenance treatment (mean 65 ± 50 mg per day, median 57 mg range [10–320]) had abnormal or prolonged QTc. Each copy of *KCNH2* Lys897Thr was associated with 15.4 ms [4.6–26.1] longer QTc.

QT interval monitoring (as suggested by Katz et al. (2013)) and a careful follow up of the other TdP risk factors (including alcohol and other drug prescriptions), or alternative treatments, such as buprenorphine or (R)-methadone, which contrarily to the S-enantiomer does not bind to hERG (Ansermot et al., 2010), could be proposed to opiate-dependent patients identified to have a higher risk of TdP.

The potential value of *KCNH2* genotyping before treatment onset should also be evaluated with a prospective blind study including extensive cardiac follow-up and repeated ECG recording.

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Contributors

All authors contributed to manuscript preparation and have approved the final manuscript.

Conflict of interest

None of the authors has any biomedical or financial conflict of interest.

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