Substitution of *(R,S)*-Methadone by *(R)*-Methadone

Impact on QTc Interval

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ABSTRACT

Background Methadone is administered as a chiral mixture of *(R,S)*-methadone. The opioid effect is mainly mediated by *(R)*-methadone, whereas *(S)*-methadone blocks the human ether-à-go-go–related gene (hERG) voltage-gated potassium channel more potently, which can cause drug-induced long QT syndrome, leading to potentially lethal ventricular tachyarrhythmias.

Methods To investigate whether substitution of *(R,S)*-methadone by *(R)*-methadone could reduce the corrected QT (QTc) interval, *(R,S)*-methadone was replaced by *(R)*-methadone (half-dose) in 39 opioid-dependent patients receiving maintenance treatment for 14 days. *(R)*-methadone was then replaced by the initial dose of *(R,S)*-methadone for 14 days (n = 29). Trough *(R)*-methadone and *(S)*-methadone plasma levels and electrocardiogram measurements were taken.

Results The Fridericia-corrected QT (QTcF) interval decreased when *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone; the median (interquartile range [IQR]) values were 423 (398-440) milliseconds (ms) and 412 (395-431) ms (P = .06) at days 0 and 14, respectively. Using a univariate mixed-effect linear model, the QTcF value decreased by a mean of −3.9 ms (95% confidence interval [CI], −7.7 to −0.2) per week (P = .04). The QTcF value increased when *(R)*-methadone was replaced by the initial dose of *(R,S)*-methadone for 14 days; median (IQR) values were 424 (398-436) ms and 424 (412-443) ms (P = .01) at days 14 and 28, respectively. The univariate model showed that the QTcF value increased by a mean of 4.7 ms (95% CI, 1.3-8.1) per week (P = .006).

Conclusions Substitution of *(R,S)*-methadone by *(R)*-methadone reduces the QTc interval value. A safer cardiac profile of *(R)*-methadone is in agreement with previous in vitro and pharmacogenetic studies. If the present results are confirmed by larger studies, *(R)*-methadone should be prescribed instead of *(R,S)*-methadone to reduce the risk of cardiac toxic effects and sudden death.

INTRODUCTION

Methadone, a synthetic μ-opioid receptor agonist, is used for maintenance treatment in opioid-dependent patients and for pain relief. Its efficacy results in reduction of drug consumption, risk for human immunodeficiency virus infection and mortality, and increase in socioprofessional rehabilitation. Methadone is widely prescribed, and its use will probably further increase owing to its recent introduction onto the World Health Organization list of essential medicines.[1] Although mainly administered as a chiral mixture of (R,S)-methadone, (R)-methadone has a 10-fold more potent agonist action on μ-opioid receptor[2] and a 50-fold higher analgesic potency[3] than (S)-methadone.

QT interval prolongation, torsades de pointes, and sudden deaths have been described in patients receiving methadone.[4-6] Safety labeling revisions have therefore been approved by the US Food and Drug Administration to notify of the risks for QT interval prolongation. Recently, cardiac safety recommendations for physicians prescribing methadone have been published.[7]

In the human heart, the human ether-à-go-go–related gene (hERG) voltage-gated potassium channel is implicated in repolarization of the cardiac action potential.[8] Mutations in *KCNH2*, the gene encoding hERG, have been associated with congenital long QT syndrome[8] and sudden death owing to malignant ventricular arrhythmias (torsades de pointes). Importantly, hERG can also be blocked by many structurally diverse drugs, including methadone,[9] causing drug-induced long QT syndrome.[10]

Methadone metabolism is mediated by several cytochrome P450 (CYP) isozymes, mainly CYP2B6 (AF182277) and CYP3A4 (AF280107),[11-14] the activities of which are genetically and environmentally determined.[11] CYP2B6 was shown to be stereoselective (approximately 1.8 fold) toward (S)-methadone in vitro,[12] which was confirmed in vivo by a pharmacogenetic study showing that CYP2B6 slow metabolizer status (the *6/*6 genotype, which represents about 6% of white individuals)[13-14] is associated with high (S)-methadone but not (R)-methadone plasma concentrations.[13-14] Of special interest is the recently demonstrated in vitro stereoselectivity block of hERG channel by (S)-methadone, which is 3.5 times more potent than (R)-methadone,[15] a stereoselectivity also confirmed by another study.[16] It was shown that, in vivo, QTc interval values were significantly higher in patients who are carriers of *CYP2B6 *6/*6* genotype than in noncarriers, owing to higher (S)-methadone plasma levels.[15]

Because only (R)-methadone has a clinical opioid activity and (S)-methadone blocks the hERG current more potently, the aim of this study was to investigate whether substitution of (R,S)-methadone by (R)-methadone could reduce the QTc interval value in opioid-dependent patients.

METHODS

STUDY DESIGN AND PATIENTS

A prospective study, including 39 opioid-dependent patients receiving *(R,S)*-methadone maintenance treatment, was conducted in Geneva (Switzerland) and Essen (Germany) from April 2006 through April 2007 (Figure 1). On the first day of the study (day 0), *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone for 14 days. For the patients included in Geneva (n = 29), the dose of *(R)*-methadone was replaced at day 14 by the initial dose of *(R,S)*-methadone and the study was conducted until day 28. For the patients included in Essen (n = 10), the observation ended at day 14. Because both *(R,S)*-methadone and *(R)*-methadone are available in Germany, the treating physician could decide on day 14 on the best treatment to continue with [7 of 10 patients, for whom the switch from *(R,S)*-methadone to *(R)*-methadone led to a QTc interval value decrease, continued with *(R)*-methadone].
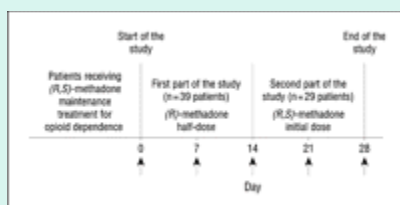
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Figure 1. Study design. Thirty-nine patients receiving *(R,S)*-methadone maintenance treatment for opioid dependence were included. At day 0, *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone during 14 days. For the patients from Geneva, Switzerland (n = 29), *(R)*-methadone was replaced at day 14 by the initial dose of *(R,S)*-methadone, and the study was conducted until day 28. For the patients from Essen, Germany (n = 10), the observation ended at day 14. The arrows indicate electrocardiogram measurements and blood samples for methadone plasma quantification.

Electrocardiogram (ECG) recording, trough *(R)*-methadone and *(S)*-methadone plasma levels, and urinary controls for opiate and cocaine were determined at baseline and each week before methadone intake. The ECG recordings were performed using a standard 12-lead digital apparatus (Cardiovit AT-1 or AT-60; Schiller AG, Baar, Switzerland). Each patient was recorded with the same apparatus throughout the study. The QT intervals values were corrected using the Fridericia-corrected formula, $QTcF = QT/(RR/1000)^{1/3}$, with QTc, QT, and RR (cycle length) expressed in milliseconds (ms). The main results were confirmed using the Bazett-corrected formula, $QTcB = QT/(RR/1000)^{1/2}$, and the Framingham-corrected formula, $QTcFram = QT + [0.154 \times (1000 - RR)]$.[17] During the study, ECGs were read immediately to exclude patients with high QTcB values (as explained later in this section), but the values were not subsequently used in the study. To avoid biases, each ECG was coded at the end of the study, mixed, and read in blind conditions with regard to time, dose, drug, and patient by a senior electrophysiologist (J.S.). The ECGs were read 2 times, and the mean value was used for the analyses. The Lin concordance correlation coefficient[18] was calculated to evaluate the agreement between the 2 series of measure. The coefficient was 0.902 (95% confidence interval [CI], 0.845-0.958), which indicates a good reproducibility of the determination. Standard 12-lead ECGs were obtained at a paper speed of 25 mm/s and a voltage of 10 mm/mV. The QT intervals were manually measured using lead II unless the T-wave morphologic characteristics were indistinct, in which case lead V5 was used.[19] Withdrawal symptom evaluations[20]; adverse opioid effects[21]; use of comedications; sodium, potassium, and calcium serum levels at baseline (measured with ion-selective electrodes [EasyLyte;

Medica, Biolabo, Châtel-St-Denis, Switzerland]); and *CYP2B6* genotyping were also determined. Methadone and electrolyte plasma levels were not measured in 5 patients who refused serial blood sampling, but one of them did provide a single blood sampling for the genetic determination.

The inclusion criteria were the following: age older than 18 years, maintenance treatment with *(R,S)*-methadone for at least 3 months before the study, no change in comedications for at least 2 weeks, and absence of self-declared consumption of cocaine or opiates for at least 1 month with at least 1 confirmatory urinary test during the past month and another urinary test during the past week. The methadone dose had to be unchanged for at least 1 week in order to be in steady state conditions. In Geneva, patients with a baseline QTcB interval value higher than 450 ms, which was considered as the upper limit of the reference range,[19] were preferentially, but not exclusively, selected. In Essen, only patients with a QTcB value of 420 ms or higher were included. Because QTcB values higher than 500 ms are considered to be a particular concern for risk of cardiac arrhythmias,[19] and owing to the exploratory profile of this study, as a safety measure, it was planned not to include patients with a baseline QTcB value greater than 500 ms and to refer them to a cardiology center (however, no patients met this exclusion criterion). Methadone dose modifications were possible during the study when facing withdrawal or overdose symptoms. Eight patients had their daily methadone dose divided into 2 intakes before the study, a splitting that was maintained during the study.

Power analysis indicated that 27 or 10 patients would be required to have an 80% power of detecting as significant a 12.4-ms[22] or 20-ms QTc difference, respectively, after substituting *(R,S)*-methadone with *(R)*-methadone, with an assumed standard deviation of 23[22] (*t* test for paired samples, 2-sided, 5% significance level) (analysis was performed using NCSS Trial and PASS2000 statistical software; NCSS, Kaysville, Utah). The protocol was approved by the local ethics committees, and written informed consent (including the genetic analyses) was obtained from all patients. In Geneva, patients received an indemnity of 400 SwF ($390); in Essen, the patients were not paid, the study being part of an evaluation of a clinical standard (quality management).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS (version 15.0; SPSS Inc, Chicago, Illinois) and Stata (version 10.1; StataCorp, College Station, Texas) statistical software. Data are presented as median (interquartile range [IQR]), mean (SD), or (95% CI) where appropriate. Normal distributions of the data were assessed using the QQ normal plot graphical method. Differences between weeks were assessed using paired-samples *t* test for QTc and RR intervals and methadone doses. Owing to the smaller number of subjects and/or nonnormal distribution, nonparametric tests were used for adverse effects and withdrawal symptoms comparison between weeks (Friedman test) and comparisons between *CYP2B6* genotypes (Mann-Whitney *U* test).

Mixed-effect linear models[23-24] were used to assess the increase or decrease of QTc interval during the study and the influence of clinical cofactors. Let QTc_{ij} be the QTc interval measured for subject *i* at $week_{ij}$, and X_{ij} be a covariate measured for subject *i* at $week_{ij}$. The covariate may change with time [like *(R,S)*-methadone plasma levels] or not (like age). In the latter case, one has $X_{ij} = X_i$ for each *j*. The mixed-effect linear model used is given by

$$QTc_{ij} = (\beta_0 + u_i) + (\beta_1 + v_i) week_{ij} + \beta_x \cdot X_{ij} + \varepsilon_{ij},$$

where β_0 (a global mean), β_1 (the effect of time on QTc interval), and β_x (the effect of the covariate on QTc interval) are fixed population parameters. Random effects u_i and v_i represent the individual deviation with respect to global intercept and slope, respectively. The term ε_{ij} represents independent measurement errors with mean zero.

Table 1 and Table 2 show bivariate associations of each independent variable with QTc interval. Starting from a model containing all significant bivariate predictors at a 20% level, nonsignificant predictors ($P > .05$) were deleted with a backward procedure selection. The resulting multivariate models are shown in Table 1 and Table 2. Interactions between all retained variables in the multivariate model were tested.

View this table: [in this window] [in a new window] [as a PowerPoint slide]	Table 1. Influence of Cofactors on QTcF Interval, When *(R,S)*-Methadone (Day 0) Was Replaced by a Half-Dose of *(R)*-Methadone (Days 7 and 14) in 39 Patients Receiving Methadone Maintenance Treatment

View this table: [in this window] [in a new window] [as a PowerPoint slide]	Table 2. Influence of Cofactors on QTcF Interval Values, When *(R)*-Methadone (Day 14) Was Replaced by the Initial Dose of *(R,S)*-Methadone (Days 21 and 28) in 29 Patients Receiving Methadone Maintenance Treatment

METHADONE ANALYSIS AND GENOTYPING

The plasma concentrations of *(R,S)*-methadone, *(R)*-methadone, and *(S)*-methadone were measured by liquid chromatography coupled with mass spectrometry.[26] The limits of quantification were 5 ng/mL for both *(R)*-methadone and *(S)*-methadone (to convert methadone to micromoles per liter, multiply by 0.00323). *CYP2B6* genotyping for allele *6* was determined by real-time polymerase chain reaction.[13]

RESULTS

PATIENTS' CHARACTERISTICS

Detailed clinical descriptions of the 39 patients included in the study are presented in Table 3. No patients were excluded for medical reasons or voluntarily withdrew, and no clinically relevant events were observed.

Table 3. Clinical Data of the 39 Included Patients Receiving *(R,S)*-Methadone Treatment

Methadone doses were not significantly modified during the study (there were minor modifications in only 6 patients). The week before the first part of the study and during weeks 1 and 2, the mean (SD) daily doses for *(R)*-methadone were 53.8 (36) mg, 54.3 (36) mg (*P* = .34), and 54.0 (36) mg (*P* = .65), respectively (n = 39 patients). For the patients included in the second part of the study, the week before this part (week 2) and during weeks 3 and 4, *(R)*-methadone daily doses were 56.2 (42) mg, 57.0 (42) mg (*P* = .14), and 57.0 (42) mg (*P* = .14), respectively (n = 29 patients). The *(R,S)*-methadone doses for the week before the study and for weeks 3 and 4 can be calculated by multiplying *(R)*-methadone doses by 2.

Opioid adverse effects and withdrawal symptoms were either absent or of low intensity and remained unchanged during the study (data not shown), which confirms that the half-dose of *(R)*-methadone is therapeutically equivalent to the racemic mixture.

Urinary controls were negative for opiate and cocaine use, except for 2 patients found to be positive for use at days 7 and 14. Comedications associated with potential QTc prolongation were not modified during the study, except for 2 patients for whom treatment with 4 drugs classified as unlikely to cause torsades de pointes[25] was stopped at day 6 but without influence on QTc values.

Trough *(R,S)*-methadone, *(R)*-methadone, and *(S)*-methadone plasma concentrations are indicated in Table 4. As expected, *(S)*-methadone plasma levels were strongly reduced at day 7 compared with day 0 ($P = 10^{-12}$), but small amounts were still present in most samples (24 of 34 individuals had levels higher than the limit of quantification). At day 14, *(S)*-methadone was detectable in only 4 of the 34 individuals. Heart rates as measured by RR interval did not vary over time (data not shown).

Table 4. Trough *(R,S)*-Methadone, *(R)*-Methadone, and *(S)*-Methadone Plasma Concentrations in Patients Receiving Methadone Treatment[a]

EFFECT OF SUBSTITUTION OF *(R,S)*-METHADONE BY *(R)*-METHADONE ON QTc INTERVAL VALUE

When *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone, median (IQR) QTcF interval values at days 0, 7, and 14 were 423 (398-440) ms, 418 (394-429) ms (*P* = .05), and 412 (395-431) ms (*P* = .06) (Figure 2A and B). The univariate model showed that the QTcF interval value decreased by a mean of −3.9 ms (95% CI, −7.7 to −

0.2) (*P* = .04) per week after replacement of *(R,S)*-methadone by a half-dose of *(R)*-methadone (n = 39) (Table 1). The multivariate model showed a significant change in QTcF value per week that depended on the potassium plasma level at baseline: expected change in QTcF value (ms) per week = −37.7 + (8.1 x potassium plasma level [mEq/L] at baseline) (*P* = .05). The median (IQR) potassium plasma levels at baseline were 4.62 (4.22-4.88) mEq/L. Patients with a potassium plasma level of 4.22, 4.62, and 4.88 mEq/L had a QTcF value change per week of −3.5, −0.3, and 1.8 ms, respectively, after replacement of *(R,S)*-methadone by *(R)*-methadone (Table 1 and Figure 2C). (To convert milliequivalents to millimoles per liter, multiply by 1.0.)
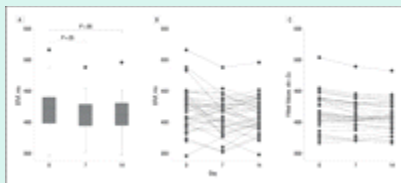
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Figure 2. Reduction of Fridericia-corrected QT (QTcF) interval values after replacement of *(R,S)*-methadone (day 0) by a half-dose of *(R)*-methadone (days 7 and 14) (n = 39 patients). Box plot (A), individual (B), and multivariate models (C) of QTcF value changes between days 0, 7, and 14. Median and quartiles are shown (bars represent the 95% confidence intervals). xb and Zu represent the linear predictors for the fixed portion and the random portion of the model, respectively.

The main results were confirmed using Bazett and Framingham formulas. Median (IQR) QTc values at days 0, 7, and 14 were 433 (420-450) ms, 430 (400-440) ms (*P* = .02), and 428 (410-447) ms (*P* = .09) with Bazett correction and 422 (399-440) ms, 418 (397-428) ms (*P* = .05), and 410 (396-431) ms (*P* = .06) with Framingham correction.

EFFECT OF REPLACEMENT OF *(R)*-METHADONE BY *(R,S)*-METHADONE ON QTc INTERVAL VALUE

When *(R)*-methadone was replaced by the initial dose of *(R,S)*-methadone, the median (IQR) QTcF values at days 14, 21, and 28 were 424 (398-436) ms, 417 (394-440) ms (*P* = .51), and 424 (412-443) ms (*P* = .01) (Figure 3A and B). The univariate model showed that the QTcF value increased significantly by a mean of 4.7 ms (95% CI, 1.3-8.1) (*P* = .006) per week after replacement of *(R)*-methadone by the initial dose of *(R,S)*-methadone (n = 29 patients) (Table 2). The multivariate model showed that QTcF interval value increased by a mean of 2.3 ms (95% CI, −2.2 to 6.8) (*P* = .32) per week, but the difference was not significant (Table 2) (Figure 3C).
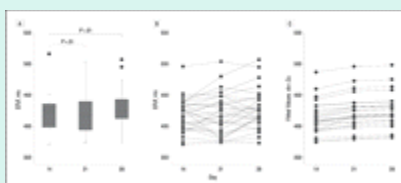
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Figure 3. Increase of Fridericia-corrected QT (QTcF) interval value after replacement of *(R)*-methadone (day 14) by the initial dose of *(R,S)*-methadone (days 21 and 28) (n = 29 patients). Box plot (A), individual (B), and multivariate models (C) of QTcF value changes between days 14, 21, and 28. Median and quartiles are shown

The main results were also confirmed using Bazett and Framingham corrections. The median (IQR) QTc values at days 14, 21, and 28 were 430 (410-450) ms, 430 (410-460) ms ($P = .50$), and 435 (420-460) ms ($P = .05$) with Bazett formula and 424 (400-432) ms, 418 (397-439) ms ($P = .49$), and 425 (413-442) ms ($P = .02$) with Framingham formula.

CLINICAL FACTORS INFLUENCING QTC INTERVAL VALUE

In the first part of the study, among the cofactors included in the univariate model, QTcF values were significantly associated with *(R,S)*-methadone daily dose, *(R,S)*-methadone plasma levels, and age, and were significantly inversely associated with calcium and potassium plasma levels at baseline (see Table 1 for *P* values). Other factors, such as body weight, sex, sodium plasma levels at baseline, use of comedications associated with QT prolongation, and being a *CYP2B6* allele *6* carrier, were not associated with QTcF values. The QTcF values were significantly higher among the patients included in Switzerland compared with those in Germany. With the multivariate model, QTcF values were significantly associated with *(R,S)*-methadone daily dose and study center and significantly inversely associated with calcium and potassium plasma levels at baseline (see Table 1 for *P* values). Similar results were obtained in the second part of the study with the univariate and multivariate analyses (Table 2).

GENETIC FACTORS INFLUENCING QTc INTERVAL VALUE

The frequency of the *CYP2B6* allele *6* was 17% (95% CI, 9%-28%; 8 heterozygous, 2 homozygous *6/*6*) and was in agreement with our previously reported value in 179 patients (22%).[15] As expected, the *(S)*-methadone/*(R)*-methadone plasma level ratio at baseline was significantly higher in carriers of allele *6* [slower metabolizers of *(S)*-methadone] (median [IQR], 1.11 [0.98-1.21]; n = 10 patients) than in noncarriers (median [IQR], 0.88 [0.73-1.06]; n = 24; $P = .03$). Higher QTcF interval values at baseline were observed in carriers of the *CYP2B6* allele *6* (n = 10 patients) compared with noncarriers (n = 25 patients); the median (IQR) values were 432 (429-449) ms and 407 (397-426) ms, respectively ($P = .05$). The median (IQR) RR intervals at baseline were not different between allele *6* carriers (0.84 seconds [0.70-0.94]) and noncarriers (0.84 seconds [0.69-0.95]; $P = .83$).

COMMENT

A significant reduction of QTcF interval value was demonstrated with the univariate model when *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone. With the multivariate model, a significant change in QTcF values was also observed, which depended on the potassium plasma level at baseline. In this model, patients with potassium plasma levels lower than 4.65 mEq/L will benefit from a QTcF value decrease after replacement of *(R,S)*-methadone by *(R)*-methadone. Withdrawal symptoms were not increased when *(R,S)*-methadone was replaced by a half-dose of *(R)*-methadone. This is in agreement with the absence of a significant contribution of *(S)*-methadone to the μ-opioid action of *(R,S)*-methadone,[2] and with a study showing that the substitution of *(R,S)*-methadone by *(R)*-methadone could be performed without influencing response to treatment.[27]

When *(R)*-methadone was replaced by the initial dose of *(R,S)*-methadone for 14 days, the univariate model showed that QTcF values were significantly increased. The increase was not significant with the multivariate analysis. The exact timing for QTc value increase after *(R,S)*-methadone treatment initiation is unknown; however, most of the prospective studies observed a prolongation of QTc interval value (mean increase, 10-14 ms) only after 2, 6, or 12 months.[22, 28] A study with 8 patients observed a mean QTc value increase of 20 ms 2 weeks after treatment initiation, unchanged after 3 and 9 months, suggesting that the onset of QTc value increase occurs during the first weeks after methadone treatment initiation.[29]

Although the Bazett correction is frequently used in clinical practice and in the medical literature, it is not an ideal correction because it overcorrects at elevated heart rates and undercorrects at heart rates below 60 beats per minute.[30] For these reasons, the Fridericia formula, which is more accurate, was chosen for this study. However, to allow closer comparison between our results and clinical and published data, in addition to the Fridericia correction, the main data were also reported using the Bazett correction, and similar results were obtained. Linear regression QT correction formulas (eg, the Framingham correction) can also be used. This formula has been shown to assess QTc interval value change with higher accuracy than the Bazett and Fridericia formulas.[17] The main analyses were repeated using the Framingham correction, and similar results were obtained.

The impact of commonly identified risk factors for developing torsades de pointes[10, 15] was evaluated by univariate and multivariate analyses of QTcF intervals. Among them, high daily dose of *(R,S)*-methadone, high *(R,S)*-methadone trough plasma concentrations, older age, and low calcium and potassium serum levels were associated with significantly higher QTcF interval values and confirmed our previous observations.[15] As expected, QTcF values were significantly higher among patients included in Switzerland compared with those included in Germany because in Geneva, patients with a baseline QTcB interval value higher than 450 ms were preferentially, but not exclusively, included. This difference between the 2 study centers has been taken into account with the multivariate analyses.

Recently, CYP2B6 stereoselectivity toward *(S)*-methadone was demonstrated in vitro[12] and confirmed in vivo.[13-14] CYP2B6 slow metabolizer status, associated with *6/*6 genotype, resulted in a reduced ability to metabolize *(S)*-methadone and was significantly associated with higher-dose normalized *(S)*-methadone plasma concentrations,[13-14] and higher QTc interval values.[15] Because CYP2B6 slow metabolizers represent about 6% of white individuals,[13] this genotype is of clinical relevance for *(R,S)*-methadone treatment. In the present study, a significantly higher *(S)*-methadone to *(R)*-trough plasma methadone level ratio and higher QTcF values at baseline were observed in patient carriers of *CYP2B6* allele *6 than in noncarriers, confirming the stereoselectivity of CYP2B6 for *(S)*-methadone and the increased risk of cardiac toxic effects in these patients.

A limitation of the present study is that it did not allow us to determine whether *(R)*-methadone could also prolong the QTc interval, even if it is less potent than *(S)*-methadone. Despite a 50% inhibitory concentration (IC_{50}) value (7μM) for hERG channel block by *(R)*-methadone that is higher than the maximum peak concentration level (C_{max}) measured in a previous study (3.65μM),[15] an intrinsic cardiotoxic effect of *(R)*-methadone, even though it has an IC_{50} higher than that of *(S)*-methadone (IC_{50} = 2μM), is possible [IC_{50}/C_{max} = 1.9 and 0.55 for *(R)*-methadone and *(S)*-methadone, respectively]. This should be examined in future studies to investigate whether a further decrease in the QTc interval could be reached after discontinuation of methadone therapy in patients receiving *(R)*-methadone, or after its substitution with drugs such as morphine sulfate or buprenorphine hydrochloride, known not to prolong,[9] or to prolong only to a small extent,[31] the QTc interval, respectively. A second limitation of this study is that, for safety reasons, no patients with a QTcB interval value at baseline greater than 500 ms were included. A third and important limitation is the low number of patients included in this study. However, an analysis showed that the study was sufficiently powered to detect the measured modifications of QTc values. Finally, our results should be validated by using more complex models for individualized QTc value determination as proposed by some authors[32] and by using digital triplicate ECGs, which are an evolving standard in new drug development.

In conclusion, the change of *(R,S)*-methadone to *(R)*-methadone reduces QTc interval values and shows, in agreement with in vitro and in vivo pharmacogenetic data, a safer cardiac profile of *(R)*-methadone compared with that of *(R,S)*-methadone. If the present results are confirmed by larger studies, *(R)*-methadone should be preferred to *(R,S)*-methadone for all patients, whether they are being treated for pain or receiving maintenance treatment for opioid dependency, in order to reduce the risk of cardiac toxic effects and sudden death. Because *(R)*-methadone is currently available only in Germany, these findings should stimulate industries to commercialize and authorities to legalize the prescription of the active enantiomer elsewhere. Prescription of *(R)*-methadone would also greatly diminish the clinical concern of CYP2B6 slow metabolizer status for cardiotoxic effects. However, until *(R)*-methadone is more widely available, the present findings should in no way limit the use of *(R,S)*-methadone when clinically indicated, but we can infer that both appropriate dosing and clinical monitoring are highly recommended.

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Author Contributions: Drs Ansermot and Eap had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.