



Swiss Society of Addiction Medicine
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Société Suisse de Médecine de l'Addiction
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Swiss Addiction Research Award (SARA) 2011

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

Impact on QTc Interval

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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.

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