QT prolongation and cardiac arrhythmic risk in a cohort of methadone treated patients

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Methadone is a synthetic opioid agonist used as replacement therapy in opioid dependence. Methadone is usually commercialized as a racemic mixture of R and S methadone enantiomers (R/S-MT). R-MT isomer accounts for the majority of its pharmacological effects on μ receptors while S-MT has a rather low affinity for opioid receptors and may even cause adverse effects (Mitchell *et al*., 2004). R/S-MT mechanism of toxicity is due to its properties in blocking repolarizing cardiac potassium channel hERG thus potentially inducing prolonged QT interval. S-MT was found to be more responsible for this effect (Eap *et al*., 2007).

The aim of this study was to determine the risk of corrected QT interval (QTc) prolongation among patients treated with R/S-MT in an opioid maintenance treatment program. We retrospectively analyzed the clinical records of 386 patients hospitalized in the Medical Toxicology Unit of Azienda Ospedaliero-Universitaria Careggi in Florence, Italy, between 2008 and 2015, evaluating the QTc with a resting 12-lead ECG. Moreover, we took into account the presence of the most common QTc prolongation co-factors (drugs, gender, clinical features and genetic factors).

We identified 64 patients (10%), with a mean QTc of 471 ms: in 3 cases QTc was superior to 500 ms. The age ranged between 16 and 78 years, male female ratio was 2:1. Twenty-four (37.5%) patients had concomitant QT-prolonging medications while 19 (29.7%) an electrolytic alteration. Only 3 patients reported both risk co-factors. No one developed fatal cardiac arrhythmia during the observation period. No correlation between dosage and QT prolongation was found.

Interestingly, the percentage of methadone treated patients with prolonged QTc was comparable to those commonly described (Fonseca *et al*., 2009).

In conclusion, since more than 90.000 patients were treated with R/S-MT replacement therapy in Italy in 2012, our results suggest that a large cohort of patients could develop QT prolongation and cardiac arrhythmic risk in a population with complicated pharmacological therapies and other important risk factors. Therefore, replacing the racemic mixture with R isomer of methadone could be a useful pharmacological strategy to reduce the risk of sudden cardiac death.

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Fonseca F., Marti-Almor J., *et al*. Prevalence of long QTc interval in methadone maintenance patients. Drug Alcohol Depend. 2009, 99:327–332.

Mitchell TB, Dyer KR, *et al*. Subjective and physiological responses among racemic-methadone maintenance patients in relation to relative (S)- vs. (R)-methadone exposure. Br J Clin Pharmacol. 2004, 58:609-17