



Tramadol linked QT interval prolongation and Torsades de pointes

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Introduction

Tramadol is a synthetic opiate drug used in the treatment of pain. It inhibits the reuptake of the aminergic neurotransmitters serotonin and noradrenaline, and has a weak μ -receptor agonist effect, through its metabolite O-desmethyltramadol [1]. Very recently in 2018 tramadol has been classified in the CredibleMeds® database (<https://www.crediblemeds.org/>) as having a possible risk of Torsades de Pointes (TdP) arrhythmia. This database is a repository of information on drugs that are associated with QT interval prolongation and Torsades de Pointes (TdP) arrhythmia, categorising drugs according to strength of evidence of causality (recently reviewed in [2]). Here I briefly consider available information linking tramadol to prolongation of the QT interval and TdP.

Abstract

Tramadol is a synthetic opiate used in the treatment of pain. This article provides a brief overview of the evidence for QT interval prolongation and Torsades De Pointes (TdP) arrhythmia with tramadol. Data from a study of patients with isolated tramadol toxicity showed rate corrected QT (QT_c) interval prolongation in ~25% of patients, whilst in a distinct study of drug-induced QT_c prolongation, QT_c prolongation was observed with tramadol, with the extent of QT_c change correlating well with plasma concentrations of the drug. Evaluation of publically available information on the EudraVigilance database of suspected adverse events found 3 cases of long QT syndrome and 7 cases of TdP with the drug. Reported ECG changes are consistent with a direct effect of tramadol on ventricular repolarisation, but there is an apparent lack of preclinical, including hERG channel, data and results from relevant *in vitro* tests would be valuable. Whilst more data on this drug are needed, the available information is sufficient to recommend that well-known risk factors for drug-induced QT_c prolongation are taken into consideration when prescribing tramadol.

Other opiate drugs, particularly methadone, have previously been associated with prolongation of the rate-corrected QT (QT_c) interval (e.g. [3,4]). In 2009, a 12 lead ECG evaluation was conducted of 100 patients with chronic, non-malignant pain, treated with methadone, oxycodone or tramadol [5]. Methadone was positively correlated with QT_c prolongation and the study established for the first time that oxycodone was associated with QT_c prolongation in a dose-dependent manner. On the other hand, tramadol dose was not associated with QT_c prolongation, though the authors noted that the small size of the tramadol treated group might conceal a QT interval prolonging effect [5]. In 2012, a study was conducted on 479 patients with isolated tramadol toxicity, in which exclusion criteria included underlying heart disease [6]. ECG analysis showed QRS widening (to 120 ms or greater) in 36 patients (7.5% of the total) and



QT_c interval prolongation (values of 440 ms or greater) in 118 patients (24.6% of the total); heart rates of >100 beats min⁻¹ were seen in 147 (30.6% of) patients [6]. Serum tramadol levels were not available in the study [6]. The authors noted that the QRS and QT_c interval prolonging effects may result from direct ion channel actions of tramadol, commenting that the drug had previously been associated with sodium channel block at high concentrations [6,7]. Whilst QRS prolongation can result in QT_c prolongation, a much greater proportion of patients in this study had QT_c than QRS prolongation, leading the authors to suggest that tramadol may have direct potassium channel inhibitory effects [6]. Virtually all drugs that prolong the QT interval inhibit *human Ether-à-go-go Related Gene (hERG)*-encoded potassium channels which underlie the cardiac rapid delayed rectifier current (I_{Kr}), a K⁺ ionic current that is critical for normal cardiac ventricular repolarisation [8,9]. Prior *in vitro* experimental data had shown that the opiates methadone and L-Alpha-Acetylmethadol (LAAM) are able to inhibit recombinant hERG channels at clinically relevant concentrations [10] and tramadol had been shown to be able inhibit neuronal delayed rectifier K⁺ channels [11]. So a direct effect on cardiac K⁺ channels is entirely plausible, though it has not been directly demonstrated.

Tramadol was subsequently associated with QT_c interval prolongation in an evaluation of drug-induced QT_c prolongation in 1270 patients [12]. Tramadol was prescribed in 1.26% of the analysed sample and was significantly associated with QT_c prolongation to >450 ms (males) and >470 ms (females), using Bazett's formula for rate correction and with changes in the QT_c interval (Δ QT_c) of > 30 ms using 4 different rate-correction formulae [12]. A targeted evaluation of tramadol by the same team has also demonstrated QT_c interval prolongation by tramadol with a clear correlation between extent of QT_c prolongation and plasma drug concentrations [13]. A Δ QT_c of >30 ms was found with each of the Bazett, Fridericia, Framingham and Hodges correction formulae. Plasma levels of 201-988 ng/ml (mean of 462 ng/ml, equivalent to 1.75 μ M) were found in patients without renal failure and of 205-1613 ng/ml (mean of 906 ng/mL, equivalent to 3.44 μ M) in patients with renal failure [13]. There was a high correlation (R>0.77) between Δ QT_c and plasma tramadol concentrations. Relative risk was analysed for different features of medical history and renal failure, but not other factors, was found to increase risk [13]. Assessment of causality using the Naranjo scale led to an evaluation of "probable" [13]. Interestingly, there were no reported instances of TdP or ventricular tachycardia during the study [13]. An independent study in 2016 detected prolonged QT_c intervals in 18.4 % of 1402 patients with tramadol poisoning and QRS widening in 6.5 % [14]. The same year a case report appeared in which a 25 year old male with multiple traumatic injuries developed ventricular tachycardia and cardiac arrest after intravenous tramadol [15]. The patient required magnesium correction and DC cardioversion and the QT_c interval on restoring sinus rhythm was 480 ms (before tramadol his QT_c interval was 320 ms). The authors suggested that tramadol may be associated with K⁺ channel related delay of repolarization [15].

Considering the foregoing literature, it is reasonable to conclude that tramadol is associated with QT_c interval prolongation, particularly at high concentrations and may, exceptionally, be associated with dangerous arrhythmia. Interrogation on 1st March 2018 of publically available information from the European Medicines Agency (EMA) EudraVigilance database of suspected adverse reactions (<http://www.adrreports.eu/en/index.html>) found 3 cases of long QT syndrome (3 females, aged be-

tween 18 and 85) and 7 cases of TdP up to February of 2018. 5 of the TdP cases were in individuals between 18 and 64 years of age, 1 was in an individual in the 65-85 years age range and the age of one person was not specified. 5 of the 7 TdP cases were females; 2 cases were fatal, 4 successfully resolved and the outcome of 1 case was unknown. Further information was not publically available, but these cases indicate that tramadol use can be associated with TdP, and potentially fatally so. A recent safety, tolerability and pharmacokinetics study using healthy subjects has been undertaken to inform design of a subsequent thorough QT/QT_c study for tramadol [16]. The outcomes of a thorough QT study on tramadol will be valuable and will usefully complement the available clinical literature. The apparent lack of preclinical data and particularly hERG channel data for tramadol is striking and the emergent clinical picture suggests that hERG and other relevant *in vitro* data are needed. In the meantime, the available information is sufficient to recommend that well known risk factors for drug-induced QT prolongation [17] are taken into account when prescribing tramadol and that some caution in respect of QT prolongation be exercised in its use, particularly in patients with renal failure.

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