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Adverse Drug Reactions

Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metaboliser

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Tramadol is a synthetic centrally-acting analgesic for the treatment of moderate to severe pain. Tramadol is generally considered to be devoid of any serious adverse effects of traditional opioid receptor agonists, such as respiratory depression and drug dependence. In most countries, tramadol is the only clinically available non – scheduled opioid. The marketed tramadol is a racemic mixture containing 50% of (+) tramadol and 50% of (-) tramadol, and is mainly metabolized to *O*-desmethyltramadol (M1) and *N*-desmethyltramadol (M2) by the cytochromes P450 CYP2B6/CYP3A4 and CYP2D6, respectively [1, 2]. The pharmacokinetic and pharmacodynamic properties of tramadol are known to be both enantioselective and influenced by the CYP2D6 phenotype [1, 3-6]. The analgesic effect of tramadol is mainly due to morphinomimetic effects, the main metabolite of the CYP2D6 pathway, (+)-M1, showing the highest affinity for μ opioid receptors [1, 7]. Accordingly, CYP2D6 ultrarapid metabolizers (UM) have been shown to produce high levels of M1 and to display a more efficient anti-nociceptive response, as well as more adverse effects, with tramadol [5, 6]. Furthermore, as synergistic anti-nociceptive mechanisms, (+)-tramadol inhibits serotonin reuptake and (-)-tramadol norepinephrine re-uptake while stimulating norepinephrine release [1, 7].

In August 2009, a 22-year-old Caucasian woman, weighing 65 kg and previously healthy, was found unconscious by her boyfriend. Repeated episodes of cardiac arrest required cardiopulmonary resuscitation and immediate ICU transfer where refractory circulatory shock was diagnosed, requiring extra corporeal circulatory support by venoarterial membrane oxygenation. The patient had hypothermia (35.5°C) and mydriasis. Echocardiography showed severe biventricular failure. Initial laboratory values showed hypoglycaemia (0.57 g/L), lactic acidosis (pH=6.85, Lactate 18 mmol/L), renal failure (creatinine 22 mg/L, urea 0.54 g/L), but normal hepatic and coagulation parameters. A routine toxicological screening of both serum and urine, at the time of ICU admission, was performed

to identify any prescribed drugs, alcohol or other poisons, and only revealed the presence of tramadol in both matrices. Despite tramadol identification, the clinical presentation did not justify the use of the mu opioid receptor antagonist naloxone at any time point. Within the first 8 h of admission, the patient developed severe liver failure with profound coagulopathy. Biological signs of liver failure abated after 36 h and continuous EEG monitoring showed no signs of hepatic or post-anoxic encephalopathy. After weaning from ECMO on day 7, the patient was discharged on day 35, and returned home without any subsequent behavioural or neurocognitive sequelae.

Repeated measurements of tramadol and its main metabolites, *O*-desmethyltramadol (M1) and *N*-desmethyltramadol (M2), were performed on 14 consecutive blood samples that were taken from admission until 168 h post admission (Figure). Tramadol, M1 and M2 measurements were performed using a validated non stereoselective liquid chromatography / tandem mass spectrometry method (LC/MS-MS) with an electrospray ionization interface in positive and multiple reaction monitoring (MRM) mode. The method used tramadol-d4 as an internal standard (IS) and two characteristic transitions for each compound (tramadol 264.4 → 58.1 and 264.4 → 264.4; M1 250.4 → 58 and 250.4 → 250.4; M2 250.4 → 44 and 250.4 → 250.4; IS 268.4 → 58.1 and 268.4 → 268.4). The calibration curves (0.5 to 500 ng/mL) were linear with good correlation coefficient ($r \geq 0.9989$) within five regression curves. The limit of quantification for each compound, defined as the lowest level where the criteria of precision and accuracy are met ($CV \leq 20\%$, $bias \leq 20\%$) was 1 ng/mL. Samples with drug concentrations > 500 ng/mL were diluted. The initial tramadol concentration was 3.22 mg/L (therapeutic range 0.1 – 0.3 mg/L), a rather low value considering the patient had reputedly ingested 4.5 g of tramadol. The apparent elimination half-life of tramadol was 3-fold longer (16 h) than the normal half-life, probably due to combined renal and hepatic failure and, accordingly, tramadol levels persisted above therapeutic concentrations for 72 h. The

calculation of the tramadol/M1 (MR1) and tramadol/M2 (MR2) metabolic ratios at all time points gave a median MR1 of 2.54 and a median MR2 of 11.4, both in accordance with ultrarapid CYP2D6 metabolism [8]. Genotyping analysis of *CYP2D6*, consisting of sequencing all exons with a previously described approach [9] and the detection of deletion/duplication alleles by TaqMan real-time PCR using a previously described method with slight modifications [10], revealed the patient to be heterozygous for a duplicated wild-type allele, giving rise to a *CYP2D6*1/CYP2D6*1X2* genotype which is predictive of a CYP2D6 UM phenotype. Additionally, we searched for deficient or inhibited CYP2B6/CYP3A4 metabolic pathways. Accordingly, the analysis of the entire coding sequence of *CYP2B6* was performed with a previously described sequencing procedure [11], and the patient was found to possess a homozygous wild-type genotype (i.e. *CYP2B6*1/CYP2B6*1*). Interestingly, ketoconazole, taken by the patient for a vaginal infection before hospital admission and a potent inhibitor of CYP3A4 and, to a lesser extent, of CYP2B6 [12, 13], was detected in the initial plasma sample at an inhibitory concentration of 200 ng/mL. Collectively, these data explain the rather low initial concentration of tramadol regarding the important dose ingested and indicate an excessive production of M1 by CYP2D6 and a rather low production of M2 by other drug metabolism pathways.

To our knowledge, this case report describes the second incidence of tramadol intoxication resulting in severe cardiac insufficiency with persistent cardiac arrest necessitating an ECMO. Daubin et al. [14] reported the first case that resulted from a combined intoxication with central nervous system depressants and suggested that tramadol ingestion alone could explain the patient's refractory shock and asystole, as the co-ingested drugs were not cardiotoxic. Interestingly, available serum concentration data from this study, especially at the time of cardiac arrest, show retrospectively a MR1 of 1.3, suggesting that the patient was likely a CYP2D6 UM. Sparse knowledge is available regarding direct tramadol

cardiotoxicity. Experimental studies have demonstrated that high doses of tramadol induce significantly depressed cardiac contractility and hypotension [15-17]. Because of the inhibition of noradrenaline reuptake, excessive blood epinephrine levels are found in CYP2D6 extensive metabolisers following tramadol ingestion, compared to poor metabolisers [4]. Moreover, the elevation in plasma epinephrine levels is highly correlated with the increase of (+)-M1 plasma concentration [4]. Consecutively to excessive tramadol ingestion, our patient, harboring a CYP2D6 UM phenotype and a partially inhibited CYP2B6 pathway, had probably experienced combined mechanisms that led to excessive circulating catecholamines. Such high circulating catecholamine levels would then explain the observed strong myocardial stunning. It is important to note that serotonin syndrome (SS) could not be suspected in the patient. Because of its central serotonin reuptake inhibition effect, tramadol has been reported to cause SS mainly in combination with selective serotonin reuptake inhibitors [18] or atypical antipsychotics [19], but uncommonly in isolated intoxication [20]. Our patient lacked specific clinical signs in favour of SS, such as hyperthermia, cognitive – behavioural changes, neuromuscular activity, seizures and right-sided heart failure.

On a follow-up visit, the patient confirmed an intentional tramadol overdose (90 X 50 mg-capsules), so as to become unwell and to obtain a medically-prescribed examination dispensation. She also admitted an ever-increasing intake of tramadol, up to 10 tablets per day, to relieve menstrual pain, as well as intermittent tramadol consumption to gain a “high” sensation. Her CYP2D6 UM phenotype could explain her apparent dependence for tramadol, as well as the severity of her clinical presentation. Although tramadol is recognized as a safe drug for the treatment of moderate to severe pain, without any major opioid-type side effects, a CYP2D6 UM phenotype, that occurs in 1-10% of Caucasians and up to 30% of certain African populations, could be a major risk factor for potentially life-threatening tramadol cardiotoxicity. Accordingly, dosage of tramadol and its main metabolite M1, advantageously

completed by CYP2D6 genotyping, could be applied to patients with excessive morphinomimetic effects in order to identify individuals at risk of tramadol-related cardiotoxicity. Tramadol treatment could then be optimized in these at-risk individuals and patient outcome and safety could consequently be improved.

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Fig Plasma levels (mg/L) of tramadol and its two main metabolites, *O*-desmethyltramadol (M1) and *N*-desmethyltramadol (M2), in 14 consecutive venous blood samples from admission until 168 hours post ICU admission, as determined by LC/MS-MS.

