Eur J Clin Microbiol Infect Dis (2007) 26:367–369
DOI 10.1007/s10096-007-0293-5

BRIEF REPORT

Methadone-induced Torsade de pointes after stopping lopinavir–ritonavir

B. Lüthi · A. Huttner · R. F. Speck · N. J. Mueller

Published online: 18 April 2007

Various drugs can cause prolongation of the QT interval in an ECG, and in rare cases this is followed by the development of potentially fatal Torsade de pointes (TdP) [1]. Since 2001, reports to the drug authorities in Europe and the USA have raised concerns that methadone may prolong the QT interval and thereby cause fatal arrhythmias. QT prolongation induced by methadone is dose-dependent. Patients treated for opioid dependence with methadone often receive concomitant medications for psychiatric disorders and infections (e.g. HIV), which allows great potential for drug–drug interactions. Described here is a case in which interruption of antiretroviral treatment triggered TdP by elevating the level of methadone in the patient's blood.

A 53-year-old HIV-positive female patient presented in December 2005 with a 2-month history of weakness, weight loss (8 kg) and fatigue. She had contracted HIV in 1992. Since July 2004 she had been on a combination antiretroviral therapy (cART) consisting of tenofovir (245 mg once daily), didanosine (250 mg once daily), fos-amprenavir (700 mg twice daily) and lopinavir–ritonavir (400 mg/100 mg twice daily). Other medications included methadone (75 mg twice daily) and methylphenidate (20 mg twice daily) for opioid dependence, and oxazepam (50 mg once daily) and paroxetin (30 mg once daily) for an anxiety disorder. Physical examination was unremarkable. Routine laboratory studies revealed a slightly elevated alanine aminotransferase level of 56 IU/l (normal <52 IU/l) and an increased lactate value of 2.9 mmol/l (normal range 0.6–2.4 mmol/l). In 2001, hepatitis C serology had been positive with an undetectable level of HCV-RNA; at this presentation it was 472,000 IU/ml and of genotype 1B. The HIV viral load was undetectable at a CD4+ cell count of 212 cells per μl.

In January 2006, the patient was seen again because of abdominal discomfort. Her lactate level had increased to 5.1 mmol/l. A presumptive diagnosis of symptomatic hyperlactatemia was made and cART was discontinued. Five days later she experienced symptomatic improvement with resolution of her abdominal pain. The lactate level had decreased to 3.3 mmol/l. Eight days after stopping cART, the patient complained of palpitations and an ECG was performed; this revealed a corrected QT interval of 654 ms (normal <450 ms in women). Electrolyte blood levels were low (potassium 3.2 mmol/l, phosphate 0.46 mmol/l, magnesium 0.77 mmol/l). The patient was admitted to the ICU on the same day and she developed TdP requiring electromechanical conversion and intubation for 48 h (Fig. 1). All oral medications were stopped and morphine was substituted for methadone. Potassium levels were kept above 5.0 mmol/l. Subsequent ECGs showed gradual normalization of the corrected QT interval, reaching a value of 420 ms after 4 days. After cART with tipranavir–ritonavir, nevirapine, tenofovir and lamivudine was resumed in February of 2006, the patient developed ascites and had to be hospitalized again. Liver biopsy revealed a fully cirrhotic liver. Despite discontinuation of cART and the initiation of supportive therapy, the patient died of complications related to liver failure.

Long QT syndrome (LQTS) is characterized by a prolonged QT interval in the ECG as well as a patient's propensity to develop syncope and experience sudden cardiac death due to the polymorphic ventricular arrhythmia called TdP. The QT interval is predominantly determined

B. Lüthi · A. Huttner · R. F. Speck · N. J. Mueller (✉)
Department of Internal Medicine,
Division of Infectious Diseases and Hospital Epidemiology,
University Hospital of Zurich,
Raemistrasse 100/RAE U 74,
8091 Zurich, Switzerland
e-mail: Nicolas.Mueller@usz.ch

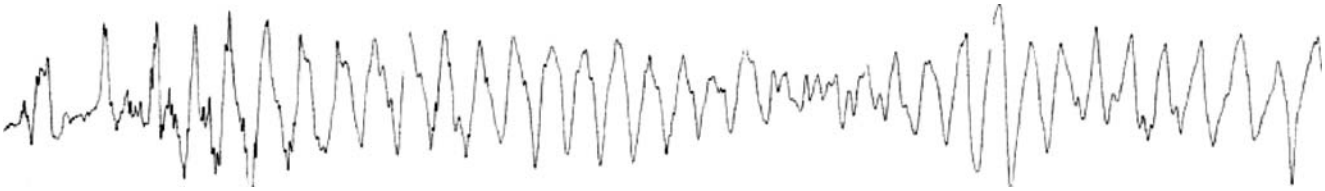

Fig. 1 Rhythm strip from the day of admission showing Torsade de pointes. QTc-time was 654 ms (corrected with the Bazett formula). Hemodynamic instability necessitated multiple cardioversions

by the duration of the action potential of ventricular cells. Genetic or acquired factors that alter the balance between inward and outward currents during the action potential significantly prolong its duration. Most drugs known to prolong the QT interval block a specific type of cardiac potassium channel expressed by the human ether-a-go-go-related gene involved in the repolarization phase of the cardiac action potential; they thus lengthen the QT interval [2]. LQTS has long been a well-known complication of anti-arrhythmic drug treatment [3]. However, a growing list of non-anti-arrhythmic drugs has been reported to cause LQTS.

Various other clinical factors have been identified that add to the risk of developing TdP, which is the most severe form of LQTS [4]. The most common is female gender (71% of cases); others include heart diseases, hypokalemia, potential drug interactions associated with the administration of two or more drugs prolonging the QT interval and high drug levels due to impaired metabolism or excessive dosage.

Methadone is a synthetic opioid frequently used in drug maintenance programs for heroin addicts. This patient population is characterized by high comorbidity, which often leads to the administration of additional antiviral as well as antibiotic drugs. Uncontrolled substance abuse is frequent, as is antipsychotic treatment. Methadone and its derivate levacetyl–methadone are the most potent inhibitors of the delayed potassium ion current in human cells among the opioid agonists, and both prolong the QT interval [5]. Methadone is mainly metabolised by the isoenzyme CYP3A4 and, to a lesser extent, by the isoenzyme CYP2D6 of the hepatic cytochrome-P450-system [6]. These pathways are also utilized by numerous antibiotics, antivirals, antihistamines, and antidepressants, all of which influence the metabolism of methadone.

The association between methadone and TdP arrhythmias was described for the first time in a case series of 17 patients in 2002 [7]. The mean dose of methadone at the time of TdP tachycardia was very high (397±283 mg/day); six patients had been prescribed a higher methadone dosage in the month prior to the development of TdP. A study by Sticherling et al. [8] reported five patients with TdP who were receiving methadone in a drug maintenance program. All of the patients had additional factors that influenced the QT time, namely, the consumption of other QT-prolonging drugs, cocaine use, taking of substances that increase the methadone level by virtue of CYP3A4 inhibition (e.g. ciprofloxacin or cocaine), or very low potassium levels. Our patient received only 150 mg of methadone daily and no new drugs had been introduced in the month prior to the final presentation.

Three of the drugs taken by our patient (methadone, paroxetine and methylphenidate) are known to prolong the QT interval. The fact that she had been on the same dosage of these three drugs for at least the preceding year without any symptoms prompted us to seek additional factors that might have triggered QT prolongation.

None of the antiretroviral drugs used by our patient are on the list of drugs that can prolong the QT interval (www.qtdrugs.org). Gil et al. [9] mention that among the HIV-infected patients treated with methadone, drug interactions have increased with the introduction of cART due to the inhibitory and/or inducing effects on cytochrome P450. The most frequently observed interaction is a decrease in the levels of methadone circulating in patients taking non-nucleoside reverse transcriptase inhibitors, and, less frequently, protease inhibitors. These drugs are occasionally stopped without any parallel decrease of the methadone doses. Two studies have examined the clinical and pharmacokinetic interactions between methadone and the protease inhibitors lopinavir and ritonavir [10, 11]. Ritonavir has been shown to inhibit CYP3A4, thereby slowing the pharmacokinetic metabolism of lopinavir and producing lopinavir levels that exceed the inhibitory concentrations for HIV [12]. Although it would be expected that the simultaneous administration of methadone with lopinavir–ritonavir would increase methadone concentrations, since it is mainly metabolized by CYP3A4, the opposite effect was demonstrated in both studies. In eight HIV-positive patients on methadone maintenance therapy, a 36% reduction in the area under the plasma concentration time curve was observed for methadone after LPV/r was introduced, and no coincident symptoms of opioid withdrawal were seen [10]. McCance-Katz et al. [11] showed a similar pharmacokinetic effect in 15 healthy individuals receiving LPV/r in addition to methadone-maintenance therapy, i.e., significant reductions in the area under the concentration time curve for methadone and a significant increase in opiate withdrawal symptoms. The researchers concluded that LPV/r leads to a net in vivo induction of metabolic clearance of methadone involving CYP3A4 and CYP2D6 and, possibly, intestinal glycoprotein P450.

We assume that the discontinuation of lopinavir–ritonavir in the case of our patient increased the level of

methadone in the blood thus precipitating the QT prolongation and near-fatal TdP. This is supported by the unusually high methadone level of 2640 nmol/l detected on the day of admission. Additional risk factors for the development of TdP in this case were hypokalemia, hypomagnesemia and female gender. Although a direct effect of antiretroviral drugs on the QT interval has not been demonstrated thus far, drug–drug interactions between methadone and antiretroviral medications have to be taken into consideration, not only when adding a new drug but also when stopping drugs that have the potential to induce drug metabolism. In the case described here, various common risk factors for TdP were present, such as female gender and electrolyte disturbances. Our patient was also treated with various QT-prolonging drugs. In this case, discontinuation of the protease inhibitor LPV/r led to an increase in the concentration of methadone since there was a lack of methadone metabolism induction.

References

1. Viskin S, Justo D, Halkin A, Zeltser D (2003) Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis 45:415–427
2. Abriel H, Schlapfer J, Keller DI, Gavillet B, Buclin T, Biollaz J, Stoller R, Kappenberger L (2004) Molecular and clinical determinants of drug-induced long QT syndrome: an iatrogenic channelopathy. Swiss Med Wkly 134:685–694
3. Tartini R, Kappenberger L, Steinbrunn W, Meyer UA (1982) Dangerous interaction between amiodarone and quinidine. Lancet 1:1327–1329
4. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S (2003) Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine (Baltimore) 82:282–290
5. Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, Ebert SN (2002) Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther 303:688–694
6. Wang JS, DeVane CL (2003) Involvement of CYP3A4, CYP2C8, and CYP2D6 in the metabolism of (R)- and (S)-methadone in vitro. Drug Metab Dispos 31:742–747
7. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS (2002) Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 137:501–504
8. Sticherling C, Schaer BA, Ammann P, Maeder M, Osswald S (2005) Methadone-induced Torsade de pointes tachycardias. Swiss Med Wkly 135:282–285
9. Gil M, Sala M, Anguera I, Chapinal O, Cervantes M, Guma JR, Segura F (2003) QT prolongation and Torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. Am J Cardiol 92:995–997
10. Clarke S, Mulcahy F, Bergin C, Reynolds H, Boyle N, Barry M, Back DJ (2002) Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir–ritonavir. Clin Infect Dis 34:1143–1145
11. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P (2003) The protease inhibitor lopinavir–ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin Infect Dis 37:476–482
12. Lea AP, Faulds D (1996) Ritonavir. Drugs 52:541–546, discussion 547–548