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Torsades de pointes tachycardia induced by common cold compound medication containing chlorpheniramine

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To the editor:

Chlorpheniramine (CPM) is a first generation histamine-receptor-1 antagonist registered in the World Health Organization Model List of Essential Medicines [1]. Due to its moderate degree of sedative effects it is frequently used as a component of compound preparations for symptomatic treatment of common cold and influenza symptoms.

CPM shows pronounced interindividual variability in pharmacokinetics, with an elimination half-life ranging from 2 to 43 hours because of its individual hepatic metabolism and the different activity of the involved cytochrome CYP2D6 which has a pronounced genetic polymorphism [2-3]. Beside this mechanism, there are still unknown metabolic pathways which are involved in the disposition of CPM in humans [2]. CPM and its metabolites are excreted pH dependent in the urine with individual excretion dosages of unchanged CPM ranging from 0% to 34% [1,4] (see also drug information).

A 40-year-old woman (63 kg body weight; BMI 21 kg/m²; Caucasian), otherwise healthy, was initially admitted to a primary care hospital after torsades de pointes tachycardia (TdP) that necessitated cardiopulmonary resuscitation. There repeated TdP was monitored (Figure 1A) in the first 24 hours after administration, which were treated successfully by magnesium infusions. At the second day after onset of TdP the patient was referred to the cardiological department of the University of Cologne for further diagnostics. Laboratory values, including creatinine were in normal ranges except mildly elevated alanine aminotransferase and aspartate aminotransferase. The main pathological finding was detected by the retrospective evaluation of the documented electrocardiogram (ECG) during the in-hospital observed TdP tachycardia: the corrected QT interval (QTc) using Bazett`s formula was prolonged up to 524 ms (Figure 1A). Therefore the diagnosis of long-QT-syndrome (LQTS) was made. The ECGs documented in our hospital revealed a borderline QTc of 440 ms (Figure 1B). All other diagnostic procedures were normal including coronary angiogram, ventriculography and complete invasive electrophysiological testing.

The patient was on no permanent medication, denied abusing any other substances, completely unremarkable on physical examination, and had no prior history of cardiac arrhythmias. She smoked regularly up to 5 cigarettes a day, drank little amounts of wine and suffered for a common cold for some days which she self-medicated with a compound medication taking two capsules three times a day. She had stopped self-medication the evening before the event. Each capsule contained 200 mg of acetaminophen, 150 mg of ascorbic acid, 25 mg of caffeine and 2.5 mg of CPM. In animal experiments CPM has been shown a dose dependent block of the delayed rectifier potassium channel $I_{Kr,}$ and to lengthen the action potential, slow cardiac repolarization and

prolong the QTc interval [5-9]. The CPM-like drug diphenhydramine also significantly prolonged QTc intervall in healthy volunteers and in patients with coronary heart diseases [10].

The coincidence between drug intake and prolongation of the QT interval in our patient is highly suggestive of CPM-induced TdP. One may speculate that the patient is a poor metabolizer with respect to CYP2D6 activity, which might have contributed to an extensive exposure, however, the patient did not agree to genotyping. The almost normal QTc interval two days after cessation of drug intake supports the causal link to CPM since serum concentration may have been decreased considerably at this time even in case of a long elimination half-life as expected for poor metabolizers.

In 1978 the putative first case of was reported. A young women on long-term thioridazine medication took a compound preparation containing CPM (Contac C®) and died due to ventricular arrhythmia [11]. The authors assumed the combination of the neuroleptic with ephedrine as fatal, but we speculate that CPM might have been played a more prominent role inducing fatal tachycardia than suspected. Indeed, thioridazine is both a substrate and inhibitor to CYP2D6, and also prolongs the QTc interval [12-14]. Concomitant medication with the two drugs thus may have resulted in a drug-drug interaction at both the pharmacokinetic and the pharmacodynamic level.

To be on the safe side, in our patient a cardioverter defibrillator was implanted and we recommended her to avoid any known QT-interval interacting medications (see list at www.azcert.org) and drugs containing CPM.

Certainly this report is limited by the missing evaluation of the initial drug concentration. Thus we cannot clarify the exact causal link between CPM intake and the occurrence of TdP. Especially, the underlying cold of the patient might have been jointly responsible for the QT prolongation [15-17].

Nonetheless it is important to report this case, because several levels of evidence suggest that second generation antihistamines interfere with the QT interval while CPM might be overlooked [18-19]. On the other hand, CPM is used worldwide in compound preparations, usually over-the-counter drugs and available for self-medication without the necessity of a prescription. In particular patients with known LQTS should avoid such compounds containing antihistamines until harmlessness in these high-risk patients has been proven.

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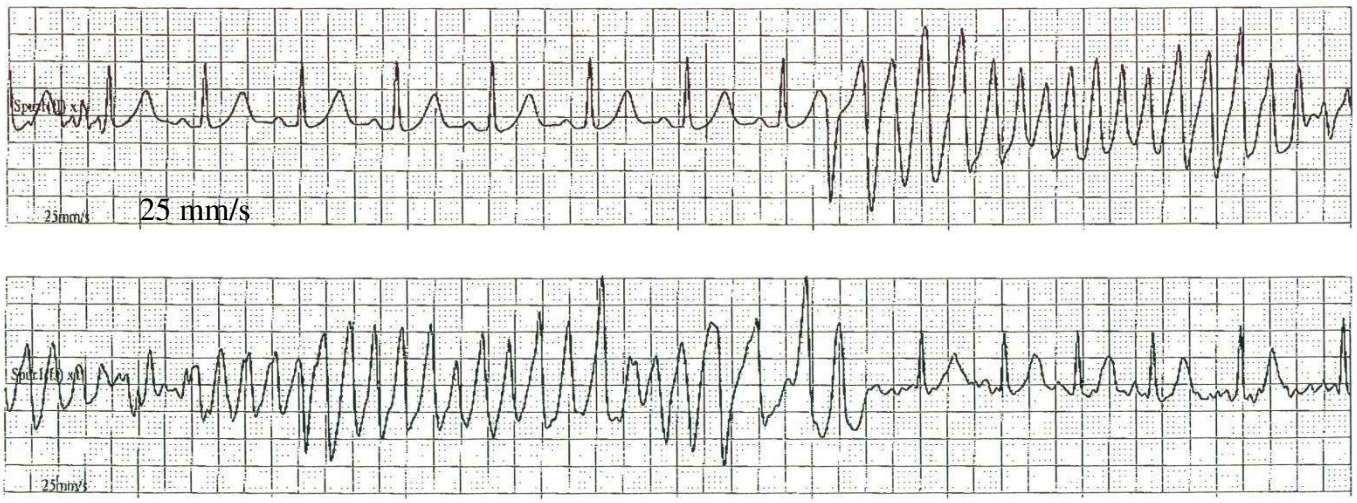
Figure legend

Figure 1. Electrocardiograms documented in the acute phase (A, 25 mm/s) with calculated QTc of 524 ms and TdP tachycardia and two days later (B, 50 mm/s) with almost normal QTc of 440 ms interval.

Figure 1

A



B