



HAL
open science

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

Amir M. Nia, Uwe Fuhr, Natig Gassanov, Erland Erdmann, Fikret Er

► To cite this version:

Amir M. Nia, Uwe Fuhr, Natig Gassanov, Erland Erdmann, Fikret Er. Torsades de pointes tachycardia induced by common cold compound medication containing chlorpheniramine. *European Journal of Clinical Pharmacology*, 2010, 66 (11), pp.1173-1175. 10.1007/s00228-010-0875-5 . hal-00612786

HAL Id: hal-00612786

<https://hal.science/hal-00612786v1>

Submitted on 31 Jul 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



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

Journal:	<i>European Journal of Clinical Pharmacology</i>
Manuscript ID:	EJCP-2010-0264
Type of submission:	Letter
Date Submitted by the Author:	16-Jul-2010
Complete List of Authors:	Nia, Amir; University of Cologne, Department of Internal Medicine III Fuhr, Uwe; University of Cologne, Department of Pharmacology Gassanov, Natig; University of Cologne, Department of Internal Medicine III Erdmann, Erland; University of Cologne, Department of Internal Medicine III Er, Fikret; University of Cologne, Department of Internal Medicine III

1
2
3
4 **Torsades de pointes tachycardia induced by common cold compound medication containing**
5
6 **chlorpheniramine**
7

8
9 Amir M. Nia¹, Uwe Fuhr², Natig Gassanov¹, Erland Erdmann¹, Fikret Er¹
10

11
12 ¹ Department of Internal Medicine III, University of Cologne, Germany
13

14
15 ² Department of Pharmacology, University of Cologne, Germany
16
17
18
19
20
21
22
23
24
25
26
27

28 **Key words:** chlorpheniramine, long QT syndrome, torsade des pointes, potassium
29 current
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 **Correspondence:**

52 Priv.-Doz. Dr. med. Fikret Er (fikret.er@uk-koeln.de)

53 Department of Internal Medicine III, University of Cologne

54 Kerpener Str. 62, 50937 Cologne, Germany

55 Phone: +49-221-47832544

56 Fax: +49-221-478 32712
57
58
59
60

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

1
2
3 prolong the QTc interval [5-9]. The CPM-like drug diphenhydramine also significantly prolonged QTc interval
4
5 in healthy volunteers and in patients with coronary heart diseases [10].
6

7 The coincidence between drug intake and prolongation of the QT interval in our patient is highly suggestive of
8
9 CPM-induced TdP. One may speculate that the patient is a poor metabolizer with respect to CYP2D6 activity,
10
11 which might have contributed to an extensive exposure, however, the patient did not agree to genotyping. The
12
13 almost normal QTc interval two days after cessation of drug intake supports the causal link to CPM since serum
14
15 concentration may have been decreased considerably at this time even in case of a long elimination half-life as
16
17 expected for poor metabolizers.
18

19 In 1978 the putative first case of was reported. A young women on long-term thioridazine medication took
20
21 a compound preparation containing CPM (Contac C[®]) and died due to ventricular arrhythmia [11]. The authors
22
23 assumed the combination of the neuroleptic with ephedrine as fatal, but we speculate that CPM might have been
24
25 played a more prominent role inducing fatal tachycardia than suspected. Indeed, thioridazine is both a substrate
26
27 and inhibitor to CYP2D6, and also prolongs the QTc interval [12-14]. Concomitant medication with the two
28
29 drugs thus may have resulted in a drug-drug interaction at both the pharmacokinetic and the pharmacodynamic
30
31 level.
32

33 To be on the safe side, in our patient a cardioverter defibrillator was implanted and we recommended her to
34
35 avoid any known QT-interval interacting medications (see list at www.azcert.org) and drugs containing CPM.
36
37 Certainly this report is limited by the missing evaluation of the initial drug concentration. Thus we cannot clarify
38
39 the exact causal link between CPM intake and the occurrence of TdP. Especially, the underlying cold of the
40
41 patient might have been jointly responsible for the QT prolongation [15-17].
42

43 Nonetheless it is important to report this case, because several levels of evidence suggest that second
44
45 generation antihistamines interfere with the QT interval while CPM might be overlooked [18-19]. On the other
46
47 hand, CPM is used worldwide in compound preparations, usually over-the-counter drugs and available for self-
48
49 medication without the necessity of a prescription. In particular patients with known LQTS should avoid such
50
51 compounds containing antihistamines until harmlessness in these high-risk patients has been proven.
52
53
54
55
56
57
58
59
60

References

1. Rumore MM (1984) Clinical pharmacokinetics of chlorpheniramine.
Drug Intell Clin Pharm 18:701-707
2. Yasuda SU, Zannikos P, Young AE, Fried KM, Wainer IW, Woosley RL (2002) The roles of CYP2D6 and stereoselectivity in the clinical pharmacokinetics of chlorpheniramine.
Br J Clin Pharmacol 53:519-525
3. Paton DM, Webster DR (1985) Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin Pharmacokinet 10:477-497
4. Huang SM, Athanikar NK, Sridhar K, Huang YC, Chiou WL (1982) Pharmacokinetics of chlorpheniramine after intravenous and oral administration in normal adults.
Eur J Clin Pharmacol 22:359-365
5. Hong HK, Jo SH (2009) Block of HERG k channel by classic histamine h(1) receptor antagonist chlorpheniramine. Korean J Physiol Pharmacol 13:215-220
6. Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF, 3rd, Guinosso PJ, Jr., Lynch JJ, Jr. (1995) Cardiac electrophysiological actions of the histamine H1-receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. Circ Res 76:110-119
7. Taglialatela M, Castaldo P, Pannaccione A, Giorgio G, Genovese A, Marone G, Annunziato L (1999) Cardiac ion channels and antihistamines: possible mechanisms of cardiotoxicity.
Clin Exp Allergy 29 Suppl 3:182-189
8. Taglialatela M, Timmerman H, Annunziato L (2000) Cardiotoxic potential and CNS effects of first-generation antihistamines. Trends Pharmacol Sci 21:52-56
9. Wang WX, Ebert SN, Liu XK, Chen YW, Drici MD, Woosley RL (1998) "Conventional" antihistamines slow cardiac repolarization in isolated perfused (Langendorff) feline hearts.
J Cardiovasc Pharmacol 32:123-128
10. Khalifa M, Drolet B, Daleau P, Lefez C, Gilbert M, Plante S, O'Hara GE, Gleeton O, Hamelin BA, Turgeon J (1999) Block of potassium currents in guinea pig ventricular myocytes and lengthening of cardiac repolarization in man by the histamine H1 receptor antagonist diphenhydramine.
J Pharmacol Exp Ther 288:858-865
11. Chouinard G, Ghadirian AM, Jones BD (1978) Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. Can Med Assoc J 119:729-731

- 1
- 2
- 3 12. Drolet B, Vincent F, Rail J, Chahine M, Deschenes D, Nadeau S, Khalifa M, Hamelin BA, Turgeon J
- 4
- 5 (1999) Thioridazine lengthens repolarization of cardiac ventricular myocytes by blocking the delayed
- 6
- 7 rectifier potassium current. *J Pharmacol Exp Ther* 288:1261-1268
- 8
- 9 13. Shin JG, Soukhova N, Flockhart DA (1999) Effect of antipsychotic drugs on human liver cytochrome
- 10
- 11 P-450 (CYP) isoforms in vitro: preferential inhibition of CYP2D6. *Drug Metab Dispos* 27:1078-1084
- 12
- 13 14. von Bahr C, Movin G, Nordin C, Liden A, Hammarlund-Udenaes M, Hedberg A, Ring H, Sjoqvist F
- 14
- 15 (1991) Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation
- 16
- 17 phenotype. *Clin Pharmacol Ther* 49:234-240
- 18
- 19 15. Pripp CM, Blomstrom P (1994) Epiglottitis and torsade de pointes tachycardia. *Br Heart J* 72:205-208
- 20
- 21 16. Silva Marques J, Veiga A, Nobrega J, Correia MJ, de Sousa J (2010) Electrical storm induced by H1N1
- 22
- 23 A influenza infection. *Europace* 12:294-295
- 24
- 25 17. Reinsch N, Buhr C, Krings P, Kaelsch H, Neuhaus K, Wieneke H, Erbel R, Neumann T (2009)
- 26
- 27 Prevalence and risk factors of prolonged QTc interval in HIV-infected patients: results of the HIV-
- 28
- 29 HEART study. *HIV Clin Trials* 10:261-268
- 30
- 31 18. Craft TM (1986) Torsade de pointes after astemizole overdose. *Br Med J (Clin Res Ed)* 292:660
- 32
- 33 19. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR, Jr. (1990) Torsades de
- 34
- 35 pointes occurring in association with terfenadine use. *JAMA* 264:2788-2790
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

1
2
3 **Figure legend**
4

5 **Figure 1.** Electrocardiograms documented in the acute phase (A, 25 mm/s) with calculated QTc of 524 ms and
6
7 TdP tachycardia and two days later (B, 50 mm/s) with almost normal QTc of 440 ms interval.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Figure 1

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

