

Over the Counter Drugs and Long QT Syndrome: Near Lethal Syncope after Cold Relief by Phenylephrine

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Abstract

Introduction: Purpose of this manuscript is a careful reconsideration concerning advantage and risk of self-medication by Over the Counter (OTC) drugs, in relationship to QTc prolongation, unrevealing concealed QT syndrome and Sudden Arrhythmia Deaths Syndrome (SADS).

Case presentation: A 64-year old lady was carried to the Emergency Department after traumatic syncope. The patient was found at home with a bruised occipital wound and retrograde amnesia; in the previous two day she had a common cold and bought an OTC (Over the Counter) formulation composed by paracetamol, ascorbic acid and phenylephrine cloridrate. ECG showed ventricular repolarization abnormality compatible with induced long QT syndrome. In the subsequent days, as phenylephrine was withdrawn, we observed a constant reduction of QT, yet still a long QTc. On the basis of clear syncope and Long QT syndrome unrevealed by phenylephrine treatment, ICD was implanted.

Conclusion: Widespread self-medication for cold relief is usually perceived as safe treatment by general population; nevertheless, in some OTC, patient could encounter medicament belonging to specific "drug to avoid list" for SADS, leading to harmful impact on prognosis.

Keywords: Long QT syndrome; Syncope; OTC; Self medication

Introduction

Syncope represents a common and interesting challenge for the cardiologist; although the majority of syncopal cases have benign origin, there is a small subgroup with concealed life-threatening disease unrevealed by accurate clinical and diagnostic work-up. Nevertheless, 12 leads Electrocardiogram (ECG) represents a cornerstone tool for the adequate clinical decision making, for both diagnostic and prognostic purpose [1]. At same time, the purpose of this manuscript is a careful reconsideration concerning advantage and risk of self-medication by over the counter (OTC) drugs [2], in relationship to QTc prolongation and concealed long QT syndrome and Sudden Arrhythmia Deaths Syndrome (SADS).

Case Presentation

A 64-year old lady was carried by her son to the Emergency Department after traumatic syncope. The patient was found at home with a bruised occipital wound and retrograde amnesia; in the previous two day she suffered a common cold and took an OTC formulation composed by Paracetamol, ascorbic acid and phenylephrine cloridrate (600 mg, 40 mg and 10 mg respectively for each dose); specifically, patient took three doses for day in the last two days. Clinical history was negative for cardiovascular events. At arrival physical examination revealed temperature 36.4°C, normal blood pressure (120/80 mmHg), rhythmic heart sounds, no heart murmur, neither rales nor leg edema. Neurological examination and *Fondus oculi* was normal. Brain Computer Tomography (CT) scan and electroencephalogram did not show any abnormality, confirmed by a subsequent brain diffusion weighted MRI. Complete blood count, serum electrolytes, renal function parameters, and glycemic level were normal. Troponin and cardiac enzymes were within normal range. ECG showed sinus rhythm, 72 bpm, normal atrioventricular conduction, slight left axis deviation and negative T wave in V1-V6 (very deep in V1-V4) and DII, DIII and aVF associated to QT prolongation (QTc 530 msec, Figure 1). A particular finding was

the presence of a clear notch on the ascending branch of negative T wave in V1-V4. Bedside echocardiogram revealed no structural heart disease and coronary angiography was normal. Patient was then admitted in Cardiology Unit and strictly monitored. Holter ECG did not reveal any arrhythmia, with long QT persistence and negative T wave in precordial leads. In the subsequent days, as phenylephrine was withdrawn, we observed a regression of negative T wave and slow reduction of QT. After discussion, on the basis of clear syncope and Long QT syndrome, Implantable Cardioverter Defibrillator (ICD) was implanted (class IIa, level B) [3]. Patient was then discharged, with carefully advice about medication to avoid (<http://www.sads.org.uk/drugs-to-avoid>; <https://crediblemeds.org/pdftemp/pdf/DrugsToAvoidList>). Two months later ECG showed still QTc prolongation (493 msec, Figure 2); the lady was asymptomatic and no arrhythmic episode was observed at device interrogation. Furthermore family screening was achieved by 12 leads ECG recording, without evidence of spontaneous phenotypic ECG prolongation among first-degree relatives; anyway they declined provocative exercise stress test and pharmacological test with epinephrine [4].

Discussion

Syncope evaluation represents always a remarkable challenge for clinicians, covering from simply vagal mediated Loss of Consciousness

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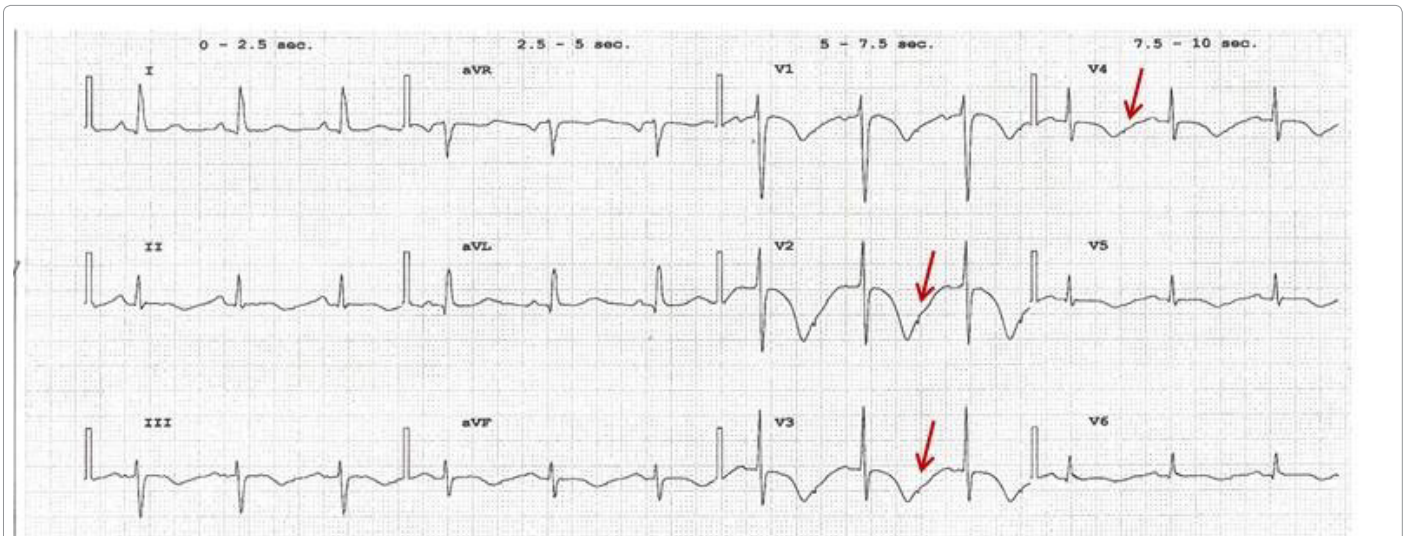


Figure 1: Admission ECG: QT prolongation, deep negative and notched T wave in V1-V4.

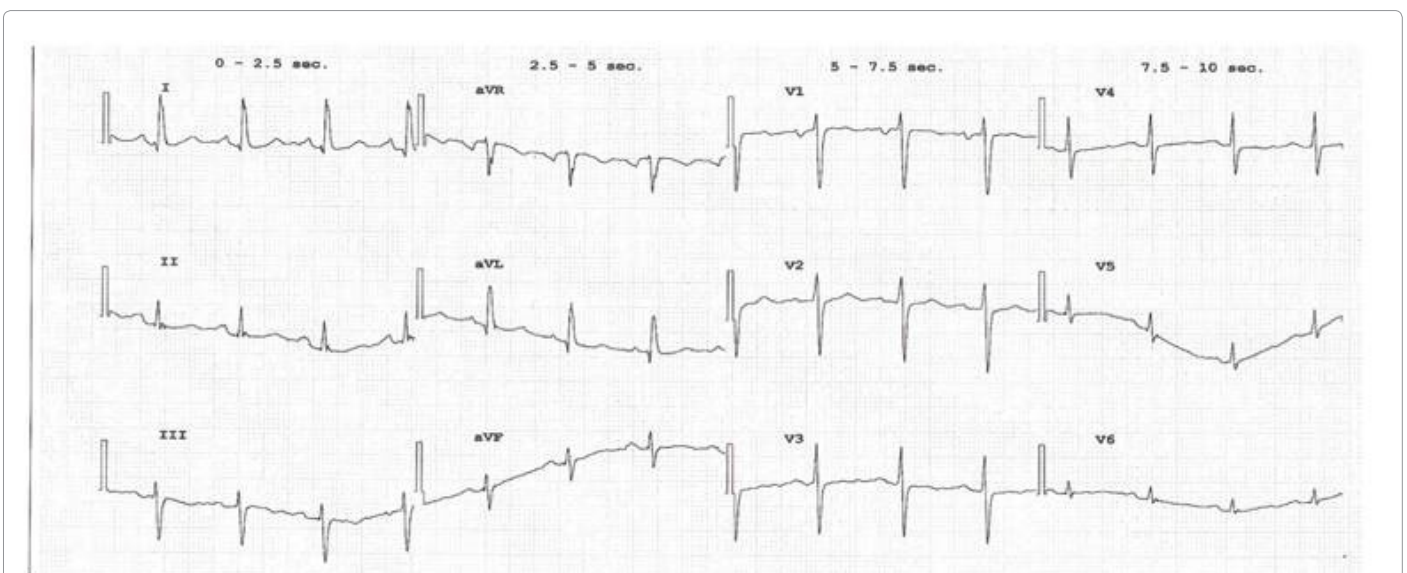


Figure 2: ECG after two months: regression on T wave abnormality, with still long QTc.

(LOC) to near aborted cardiac arrest; anyway, electrocardiogram represents a cornerstone tool for the diagnosis and management of patients affected by LOC, as in case of inherited arrhythmia syndromes [1]. Long QT Syndrome (LQTS) is a repolarization disorder with iatrogenic and/or genetic etiologies that may cause recurrent syncope, life-threatening tachyarrhythmias and sudden cardiac death [5]. The key characteristics of clinical presentation are ECG abnormality and history of syncope. In our patient we observed QTc prolongation (493 msec) two months after drug withdrawal, notched T wave at admission ECG and syncope without stress, fulfilling the *Schwartz score* for Long QT Syndrome diagnosis (3, 1 and 1 respectively, with a score of 5, high probability); QTc calculation was made by using *Bazett's correction* [6], as recommended by Schwartz and Ackerman [7]. Since the lady had no family history for sudden cardiac death, neither cardiovascular risk factor to be addressed by cardiologic evaluation, she was never undergone ECG analysis that could reveal any proarrhythmic disease. After admission, on the basis of persistent QT prolongation

despite phenylephrine withdrawal, clinical history of traumatic loss of consciousness and the particular ECG finding of notched negative T wave, we implanted an ICD, according to current guidelines [3]. In this patient, typical clues have allowed a straightforward decision-making process; more commonly, borderline cases require integration of multiple investigations represented by besides clinical history, rest ECG, QT analysis during 24 hours Holter ECG, genetic analysis and provocative test, for instance exercise test (with QTc analysis during recovery) and epinephrine [8]. The appropriate high risk evaluation for sudden cardiac deaths assumes a relevant value for the proper ICD implantation in primary prevention, for both patients and their first-degree relatives. Genetic forms of LQTS are determined by mutations of the genes encoding for transmembrane ion channels, while iatrogenic forms are more often related to electrolyte imbalances and drugs, mainly due to inhibition of the hERG potassium channel. In both case, a QT prolongation leads to arrhythmia as *Torsades de Pointes* (TdP) and consequent syncope, till possible ventricular

fibrillation and sudden cardiac death [9]. Several drugs are implicated in QT prolongation, other than antiarrhythmic (e.g. quinidine, sotalol, and flecainide, as definitely reported in SWORD [10] and CAST [11] trials), such as antibiotics, antihistamines, antipsychotics, antiemetics, antineoplastics and many others. The drug effect on cardiac repolarization added to patient genetic predisposition may unreveal otherwise clinical concealed LQTS. This finding underlines the role of pharmacogenetic in clinical practice and drug development [12]. Since the iatrogenic QT prolongation consciousness arises, upsetting the balance between risk and benefit in drug prescription, tight controls are been applied in both daily practice and new drug approval [13]. In the past, pharmacological treatment has been chiefly mediated by physician, on the basis of patient examination and history, avoiding useless and harmful prescriptions. In the last years, as self-medication arises on the basis of patients' requirement, the patient-physician relationship has been transferred to pharmacist-patient interaction; in this regard, OTC represent efficient drugs available without prescription, on the basis of self-assessment, however requiring a safe profile warranty [14]. Nevertheless, substances like phenylephrine, commonly available among OTC compositions, belong to clearly defined "drug to avoid list" for Sudden Arrhythmia Deaths Syndrome (SADS). Phenylephrine is an alpha-adrenergic agonist, mainly prescribed for cold relief and symptomatic hypotension; despite beta-adrenergic agonists, as epinephrine, are directly correlated to QT prolongation in LQTS mutation carriers (epinephrine test in LQTS management) [7], also phenylephrine is associated to QT prolongation and ventricular arrhythmias. Therefore, a strict patient and symptoms surveillance together with an ECG acquisition, at least once, is of paramount meaning in OTC trading, leading to proper safety and preventing fatal accident in daily self-medication.

Conclusion

Widespread self-medication for cold relief is usually perceived as safe treatment by general population; nevertheless, in some OTC, patients may encounter medicaments belonging to specific "drug to avoid list" for Sudden Arrhythmia Deaths Syndrome, leading to harmful impact on prognosis. An extensive awareness of this critical issue by pharmacists together with a better population screening for sudden death risk (ECG recording once in a lifetime) could improve self-medication advantages, avoiding unacceptable fatalities.

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