Opinion

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When Prescribing Pain Medications, Think About Qtc Index

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In our practice, we have prescribed amitriptyline thousands of times, but how often have we thought about checking QTc index before doing it?

The QT interval in the electrocardiogram is the expression of ventricular repolarisation, it is variable in the general population and highly dependent upon heart frequency; therefore, in clinical practice, the QTc index is used, to correct for heart frequency through the well-known Bazzett's correction formula ($QTc=QT/RR^{0.5}$) for heart frequencies below 90 bpm. The QTc index is considered normal when below 450 milliseconds (ms) in men and 470 in women, a considerable risk to develop polymorphic ventricular tachycardia named "Torsade de pointes" (TdP) is possible when QTc is over 500 milliseconds. Symptoms can be either dramatic, like loss of consciousness or seizures, or mild like vertigo, lypothymia, palpitations or sensation of light-headedness. In both cases there is a sensible risk of ventricular fibrillation and sudden death. Nevertheless, TdP does not always lead to ventricular fibrillation, but is more often so when QTc prolongation is reached in a short amount of time, therefore it is very important to check baseline ECG before prescribing drugs with know QTc prolongation effect. In fact, although the congenital long-QT syndrome, a genetic disease with mutation of the potassium cardiac channels, is rare, still it could affect 1 in 10000 individuals and cause as many as 3000 deaths (mostly children and young adults) in the USA per year [1].

Drugs that more easily lead to TdP are class IC and III antiarrhythmic, where a correlation between the risk of developing TdP and extent of QTc prolongation has been found. Conversely, other dose-dependent QTc prolonging drugs like amitriptyline and neuroleptics, do not necessarily elevate the risk *per se* [2,3]. It is important to underline that individual and environmental factors also play a role, namely: age over 65 years, female sex, myocardial hypertrophy (hypertension), congenital long QT syndrome, bradycardia, electrolyte disturbances, high plasma concentrations of drugs (overdose, intoxication or drug-drug interactions, rapid infusion of the drug or hepatic renal insufficiency) [4]. Also, when two or more additional risk factors are concomitant, drug-induced TdP develops in 85% of the 77 patients reported in a recent study [5].

There is a considerable number of non-cardiac medications that cause a prolongation of the QTc index: many of these are either drugs prescribed to treat chronic pain and primary headache (opioids, antidepressants and neuroleptics) or for trivial symptoms like nausea (domperidone, metoclopramide and prochlorperazine), allergies or flu (antihistamines, ephedrine) and diarrhoea (loperamide). Methadone and lithium (the latter is first line treatment for chronic cluster headache) are described to be at higher risk to cause TdP, while other commonly prescribed drugs like quetiapine, tricyclic antidepressant, selective serotonin/noradrenaline re-uptake inhibitors, opioids, can prolong QTc but rarely cause major arrhythmias [6]. Nevertheless, in clinical practice we often offer multiple pharmacological options to our pain patients, in order to treat comorbid conditions (e.g. depression and migraine) and acute symptoms (like headache and nausea); furthermore, polytherapy has been described to raise the risk of TdP in psychiatric patients [7]. Therefore, it is strongly advisable to check a recent ECG or, alternatively, an historical QTc in order to take care of possible genetic long QTc syndrome.

Other symptomatic treatment for migraine have been recently reported to cause QTc prolongation through cardiac vasoconstriction [8], therefore, it is very important to check and follow-up cluster headache patients treated with lithium, verapamil and subcutaneous sumatriptan, migraine patients treated with betablockers, amitriptyline and triptans. Other special conditions to take care of, when prescribing pain medications, are patients with Parkinson's disease or Helicobacter pylori infections. In fact, the former could already take amantadine and domperidone while the latter are likely to be prescribed macrolides, quinolones, proton pump inhibitors and cisapride, all well-known drugs to determine TdP.

Monitoring QTc index over time is also advisable when polytherapy with certain QTc prolongation effect is prescribed and/or risk factors (mentioned above) are present.

Drug-induced QTc prolongation can happen more often than we think, fortunately it rarely causes ventricular tachyarrhythmia "so called" TdP, that in turn, is usually a self-limited phenomenon but also can lead to ventricular fibrillation and sudden cardiac death. Although the genetic syndrome of prolonged QT is a rare disease, it is highly recommended to exclude a genetically high QTc index at baseline, before prescribing any medication known to be prolonging QTc. The first case of Torsade de Pointes, caused by therapeutic doses of citalopram, was recently reported in a 40-year-old woman admitted to the emergency department, referring syncope preceded by palpitation: her QTc was initially of 535 ms and during hospitalisation she developed TdP. The patient was later discharged with a diagnosis of long QT syndrome [9].

Conclusion

In conclusion, we can confirm that drug-induced TdP is a rare event, but we ought to think about possible QTc prolongation effect caused by our prescriptions to patients with chronic pain for several reasons: polytherapy and drug-drug interactions, comorbid diseases, patient's age and sex, cardiac diseases, use of diuretics, long QT syndrome.

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