QT prolongation and torsades de pointes with psychotropic agents

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ABSTRACT

The unexpected and catastrophic cardiovascular effects of psychotropic drugs are well described albeit uncommon. The list of drugs which have been associated with prolonging QT interval and hence potentially causing Torsades de pointes is exhaustive. The insight into the plausible mechanisms are largely unclear. However, the practical implications of anticipating and recognizing QT prolongation cannot be overemphasized.

Key words: Psychotropic agents, QT interval, torsades de pointes

INTRODUCTION

Many drugs are notoriously known to prolong the QT interval, especially those used in cardiology and psychiatry practice. QT prolongation can remain asymptomatic or lead to torsades de pointes (TdP), a rare tachyarrhythmia which can be life-threatening or nearly fatal due to ventricular fibrillation and sudden cardiac death. In 2005, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) published guidelines to evaluate QT interval prolongation and pro-arrhythmic potential of nonantiarrhythmic drugs (ICH-E14).[1] With few exceptions, all new drugs entering the market have to undergo a “thorough QT study” (TQT) defined by the ICH-E14.[1,2] However, a majority of the presently used drugs were marketed before TQT studies were made mandatory. In addition, even a well-performed TQT study cannot rule out the pro-arrhythmic potential of the drug when used in different clinical situations, as in comorbid heart disease, substance abuse, and self medication with over-the-counter drugs and drug-drug interactions due to polypharmacy.

THE QT INTERVAL

The QT duration is a measure of the cardiac electrical cycle. It includes both ventricular depolarization and repolarization.[3] Repolarization is shortened in tachycardia and hence, a correction of the observed QT to the heart rate is to be applied. Normally, over a 24 h period, intra individual variability of the corrected QT (QTc) is anywhere from 76 to 102 ms.[3]

CALCULATION OF QT INTERVAL AND CORRECTED QT

The QT interval is the duration between the beginning of the q wave to the end of the t wave in the surface electrocardiogram (ECG), taken usually in limb lead II as an average of measurements from at least 3 to 5 complexes.[4] In case it is not possible, other alternate limb and chest leads have also been recommended. For better measurement of the QT interval, some authorities have used a total of 6
leads, including 3 limb leads and 3 chest leads, and the median of the 6 individual leads as the QT value.\[9\]

**CALCULATION OF THE CORRECTED QT**

As repolarization is faster when the heart beats more rapidly, the QT interval should also be corrected for the heart rate. For calculating the QTc interval, most commonly Bazett’s square root formula \(QTc = QT/RR^{0.5}\) is used and is recommended for relatively low heart rates (60–80 bpm). The Fridericia cube root formula \(QTc = QT/RR^{0.33}\) is suitable for higher heart rates.\[3\] Isbister’s QT–heart rate nomogram (QT nomogram) may also be used for this purpose.\[4\]

The upper limit of the normal reference QTc intervals for males is 450 ms and that for females is 460 ms. There is considerable intra-individual variability of the QTc up to 76–102 ms over the course of 24 h. QTc intervals longer than 500 ms are a major risk factor for the development of TdP.\[6\]

**MECHANISM OF CORRECTED QT PROLONGATION**

Drugs prolonging QT interval bind to the cardiac potassium channels (IKr, also known as human ether-a-go-go related gene channels), usually the rapid component of the delayed rectifier potassium channel leading to a blockade of potassium efflux from cardiac myocytes. Hence, ICH-E14 guideline reiterates the importance of in-vitro IKr inhibition assay.\[1\] Some authorities have recommended using the multiple ion channel effects approach in evaluating the pro-arrhythmic risk of new drugs as false-positive results are fewer.\[7\]

Classic antipsychotic drugs and tricyclic antidepressants may induce dose-dependent QT prolongation which may not necessarily result in TdP.\[8\] Certain cardiac drugs such as sotalol, flecainide, propafenone (class IC and class III antiarrhythmic drugs) may induce TdP in accordance with the extent of prolongation of the QT interval, which may not be the case with other repolarization-prolonging drugs.\[8\]

**RISK FACTORS FOR QT PROLONGATION AND TORSADES DE POINTES**

Many factors may influence QT interval and may in turn predispose to TdP\[8-11\] (see infra).

- Age over 65 years
- Female sex (longer QTc interval than men and twice the risk of drug-induced TdP)
- Increased myocardial mass (e.g., in arterial hypertension)
- Congenital QT prolongation syndrome
- Bradycardia
- Electrolyte disturbances (hypokalemia, hypomagnesemia)
- Preexisting heart disease
- High plasma concentrations of the drug
- Inhibition of drug metabolism by concomitantly administered drugs
- Reduced drug clearance due to renal or hepatic insufficiency, or due to rapid infusion of the drug
- Polymorphisms of genes coding ion channels or enzymes involved in drug metabolism.

Considerable variation between antipsychotic drugs can be expected, possibly due to the differences in affinity of the drugs to different receptors. The risk of TdP is dose-dependent, though its occurrence cannot be predicted within the therapeutic range. Though a drug, by itself may not cause QT prolongation and TdP when used individually, concomitant use of other QT prolonging drugs and/or other risk factors as referred to above, can significantly increase the risk of TdP. Both oral and parenteral psychotropic agents have been associated with the risk of QT prolongation, the risk being higher with high dose IV medications as available evidence suggests.\[11\]

**STATUS OF CURRENTLY USED PSYCHOTROPIC AGENT CLASSES AND THEIR RISK OF INDUCING CORRECTED QT PROLONGATION AND TORSADES DE POINTES**

**Antipsychotics**

Among the antipsychotics, though the newer atypical antipsychotics were considered to be more cardio safe than the typical ones, studies have negated this belief and reported similarly increased risks of sudden cardiac deaths. Patients on aripiprazole,\[12\] olanzapine,\[13\] and perphenazine,\[13\] are reported to be at low risk while those on amisulpride,\[13\] clozapine,\[13\] flupenthixol,\[13\] levomepromazine,\[13\] sulpiride,\[13\] quetiapine,\[13\] paliperidone,\[14\] and risperidone,\[14\] are at moderate risk. Those on chlorpromazine,\[13\] haloperidol,\[13\] pimozide,\[15\] sertindole,\[16\] and ziprasidone\[17\] are at high risk of QTc prolongation, the risk being highest with thioridazine.\[13\]

**Antidepressants**

Among tricyclics and mono amine oxidase inhibitors, mirtazapine\[18\] has least risk while amitriptyline,\[19\] clomipramine, doxepin,\[20\] imipramine, moclobemide, nortriptyline,\[21\] fluoxetine, venlafaxine, and paroxetine\[22\] are reported to be at a moderate risk of QTc prolongation. Citalopram,\[19\] duloxetine,\[23\] and escitalopram,\[19\] carry a moderate risk while most of the selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors such as - bupropion,\[19\] desvenlafaxine, levomilnacipran, mianserin, sertraline, vilazodone\[24\] and reboxetine\[25\] are
reported to be safe with a low risk of QTc prolongation at therapeutic doses.

Mood stabilizers
Among the mood stabilizers, lithium\[22\] has a moderate risk of QTc prolongation while the antiepileptics used for this purpose such as carbamazepine, oxcarbazepine, topiramate, valproate,\[26\] pregabalin, gabapentin,\[27\] and lamotrigine\[28\] are reported to be safe with a low risk of QTc prolongation.

Anxiolytics and sedatives
Most of the benzodiazepines are reported to be safe with a low risk of inducing QTc prolongation.\[13\]

Anticholinergics
Among the anticholinergic drugs, biperiden, orphenadrine, and trihexiphenidyl are relatively safe with a low risk.\[13\]

OPIOID AGONISTS
Among opioid substitutes, methadone has been reported to have a moderate risk, while buprenorphine is relatively safe with a low risk of QTc prolongation in patients.\[29\]

QT prolongation has been reported with the usage of nearly all psychotropic drugs. However, TdP is rare. The clinician should have a fair knowledge of the risk posed by the drugs prescribed by him/her in medical practice; in this context, that of QTc prolongation and the risk of TdP.

CONCLUSION
No drug is totally safe. Every patient is unique and so is his/ her response to any drug. Individualization of treatment is the greatest challenge for the attending clinician whose role is pivotal in selecting the right drug for the right patient. It can be recommended to perform an ECG to record the QT interval at baseline, after introduction of the psychotropic agent, and to be repeated in an event that may be suspected to alter the QT interval. Polypharmacy and over-the-counter self-medication being rampant, can compound the problem. A simple approach is being vigilant on the patient’s new symptom or change in QTc on ECG review should alert the clinician to withdraw the offending drugs to prevent a catastrophe.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs; availability. Fed Regist 2005;70:61134-5.
2. Stockbridge N, Morganroth J, Shah RR, Garnett C. Dealing with global safety issues: Was the response to QT-liability of non-cardiac drugs well coordinated? Drug Saf 2013;36:167-82.
3. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsades de points. Am Heart J 2007;153:891-9.
4. Isbister GK, Page CB. Drug induced QT prolongation: The measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol 2013;76:48-57.
5. Beach SR, Celano CM, Nouseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics 2013;54:1-13.
6. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-22.
7. Kramer J, Obejero-Paz CA, Myatt G, Kuryshay EA, Bruening-Wright A, Verducci JS, et al. MICE models: Superior to the HERG model in predicting torsade de pointes. Sci Rep 2013;3:2100.
8. Allmann D, Eggmann U, Ammann P. Drug induced QT prolongation. Wien Klin Wochenschr 2008;120:128-35.
9. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000;355:1048-50.
10. Van Noord C, Straus SM, Sturkenboom MC, Hofman A, Aarnoudse AJ, Bagnardi V, et al. Psychotropic drugs associated with corrected QT interval prolongation. J Clin Psychopharmacol 2009;29:9-15.
11. Stilberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. Int Clin Psychopharmacol 2008;23:243-51.
12. Dhillon S. Araiprazole: A review of its use in the management of mania in adults with bipolar I disorder. Drugs 2012;72:133-62.
13. Ozeki Y, Fuji K, Kurimoto N, Yamada N, Okawa M, Aoki T, et al. QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:401-5.
14. Gopal S, Hough D, Karcher K, Muanah I, Palumbo J, Berlin JA, et al. Risk of cardiovascular morbidity with risperidone or paliperidone treatment: Analysis of 64 randomized, double-blind trials. J Clin Psychopharmacol 2013;33:157-61.
15. Zemrak WR, Kenna GA. Association of antipsychotic and antidepressant drugs with QT-T interval prolongation. Am J Health Syst Pharm 2008;65:1029-38.
16. Nielsen J, Wang F, Graff C, Kanters JK. QT dynamics during treatment with sertindole. Ther Adv Psychopharmacol 2015;5:26-31.
17. Potkin SG, Presskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of oliperiden including metabolic inhibition via CYP2D6 and/ or CYP3A4 and a comparison to quetiapine and ziprasidone. J Clin Psychopharmacol 2013;33:333-10.
18. Spindelegger CJ, Papageorgiou K, Grohmann R, Engel R, Greil W, Konstantinidis A, et al. Cardiovascular adverse reactions during antidepressant treatment: A drug surveillance report of German-speaking countries between 1993 and 2010. Int J Neuropsychopharmacol 2014;18:1-9.
19. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: A cross sectional study of electronic health records. BMJ 2013;346:f2888.
20. Mansbach RS, Ludlington E, Rogowski R, Kittrelle JP, Joehelson P. A placebo- and active-controlled assessment of 6- and 50-mg oral doxepin on cardiac repolarization in healthy volunteers: A thorough QT evaluation. Clin Ther 2011;33:851-62.
21. Jeon SH, Jaekal J, Lee SH, Choi BH, Kim KS, Jeong HS, et al. Effects of nortriptyline on QT prolongation: A safety pharmacology study. Hum Exp Toxicol 2011;30:1649-56.
22. Wiensz-Beinfert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011;108:687-93.
23. Zhang L, Chappell J, Gonzales CR, Small D, Knadler MP, Callaghan JT, et al. QT effects of duloxetine at supratherapeutic doses: A placebo and positive controlled study. J Cardiovasc Pharmacol 2007;49:146-53.
24. Jasiak NM, Bostwick JR. Risk of QTc/QT prolongation among newer non-SSRI antidepressants. Ann Pharmacother 2014;48:1620-8.
25. Fleishaker JC, Francom SF, Herman BD, Knuth DW, Azie NE. Lack of effect of reboxetine on cardiac repolarization. Clin Pharmacol Ther 2001;70:261-9.
26. Kwon S, Lee S, Hyun M, Choe BH, Kim Y, Park W, et al. The potential for QT prolongation by antiepileptic drugs in children. Pediatr Neurol 2004;30:99-101.
27. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, et al. Lamotrigine does not prolong QTc in a thorough QTc/QT study in healthy subjects. Br J Clin Pharmacol 2008;66:396-404.
28. Chen D, Lai R, Zomorodi K, Atluri H, Ho J, Luo W, et al. Evaluation of gabapentin enacarbil on cardiac repolarization: A randomized, double-blind, placebo- and active-controlled, crossover thorough QT/QTc study in healthy adults. Clin Ther 2012;34:351-62.e3.

29. Fareed A, Patil D, Scheinberg K, Blackinton Gale R, Vayalapalli S, Casarella J, et al. Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: A 5-year follow-up. J Addict Dis 2013;32:244-51.