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SPECIAL ARTICLE

Citalopram, escitalopram and prolonged QT: Warning or alarm?☆

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Abstract The alerts issued by Regulatory Agencies on the potential cardiac toxicity of citalopram and escitalopram have caused alarm among clinicians. A review of the data concerning this topic shows that the alarm should be limited to patients with a history of syncope or poisoning. As a precautionary measure, an electrocardiogram should be performed on elderly patients.

PALABRAS CLAVE
Citalopram;
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Citalopram, escitalopram y QT largo: ¿alerta o alarma?

Resumen Las alertas generadas por las Agencias reguladoras acerca de la posible toxicidad cardíaca del citalopram y escitalopram han generado alarma entre los clínicos prescriptores. La revisión de los datos acerca de la mencionada toxicidad evidencian que debe limitarse a pacientes con historia clínica de sincopes o en casos de intoxicación. Como medida de precaución debería introducirse la realización de un electrocardiograma en pacientes de edad avanzada.

Long QT syndrome (LQTS) is a cardiac disorder caused by a lengthening in the repolarization phase of ventricular action potential. In short, it is caused by a dysfunction in the activity of potassium (K) ionophores during this phase. Normal depolarization is produced by rapid entry of positive changes, specifically sodium (Na) and calcium (Ca) ions, into a myocardial cell. The drop in positive charges that initiates repolarization occurs when the output of K ions exceeds the entry of sodium and calcium mentioned. When K output is deficient or slow, repolarization takes longer; this can be seen in an electrocardiogram (ECG) with the lengthening of the QT interval (LQTS). The LQTS syndrome involves an increase in the risk of serious ventricular arrhythmia. This syndrome can be congenital, due to a ''channelopathy'', or acquired, and generally drug-induced as well; in that case, it is called only long QT (LQT). This type of case is what

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has supposedly worried millions of patients in the USA and Europe through their respective physicians alerted by the regulatory agencies (the US Food and Drug Administration, FDA, and the European Medicines Agency, EMA) with respect to citalopram and escitalopram, 2 of the selective serotonin reuptake inhibitors (SSRI) antidepressants most commonly used in our setting.

There are certain diagnostic criteria for LQTS. Every factor of risk and each of the alterations that the ECG can present is scored according to their weight in the diagnosis. These run from the 2 points for history of fainting spells in the context of stress, passing through 1 point for relatives diagnosed with LQTS, up to a growing figure based on the length of the QT (2 points between 460 and 470 ms of QT).[1]

The capacity of an antidepressant drug to induce this type of effect on the myocardium is unrelated to its main pharmacodynamic action, which is to antagonise synaptic structures such as amine transporters, receptors, self-receptors and even metabolizing enzymes. The mechanism that alters the speed of potassium output during repolarization depends on the action of the drug on the proteins that surround the potassium ionophore and regulate its opening. Drugs that interfere with this mechanism, reducing or making such opening more difficult, can potentially hinder repolarization and lengthen the QT interval on the ECG.

In August 2011, the FDA warned that citalopram should not be prescribed in doses higher than 40 mg a day in young adults, and no more than 20 mg daily in individuals older than 60 years, due to the possible induction of electrical abnormalities in the ECG. The reasons advanced by this regulatory agency are based on the communication of cases to the agency itself and on an unpublished double blind controlled drug surveillance study, with healthy subjects who took citalopram in doses from 20 to 60 mg, as well as escitalopram in equivalent ranges.[2] This alert, initially shared by the EMA,[3] was qualified in 2012; the FDA changed the term ''contraindicated'' to ''not recommended'', intimating that some patients at risk could benefit from low doses citalopram.[4] As for preclinical references, there are data showing that citalopram lengthened QT in Beagle dogs; but the plasma levels were considerably higher than in humans.[5]

With respect to studies in international literature, the data are more controversial in relation to the FDA alert. In contrast to the non-transparency of the data from the US agency, a meta-analysis[6] of 40 clinical trials on citalopram efficacy, including doses between 5 and 60 mg/day, evidenced that citalopram can lead to a reduction of a mean of approximately 8 beats in cardiac frequency without any significant effect on QT interval.

In a study[7] on patients who took an overdose of escitalopram and were admitted to emergency services, no very alarming data were found either. There were 34 patients who took up to a maximum of 560 mg of escitalopram. Effects detected were some cases of minor serotoninergic syndrome, bradycardia in 11 patients, tachycardia in 33, and hypotension in 8 patients, while a QT ''of risk'' was found in 11 cases. There were no cases of arrhythmia, convulsions or death.

A study[8] on the population that received treatment in 2 large United States hospitals was published in January 2013. From among all the individuals treated between 1990 and 2011, all the patients who had received an ECG after being prescribed an antidepressant were selected. The study revealed a modest but significant relationship between the dose of citalopram and escitalopram (in addition to amitriptyline) and QT. However, the biases involved in this methodology make it difficult to reach conclusions. The patients who received a cardiac examination were those that the clinician assessed as being at greatest cardiac risk, given that it was not a prospective study or one that related the concentration in blood with QT.

The study that offers undoubtedly more reliable information is that published by Zivin et al.[9] In that study on the population treated in Veterans Health Administration centres between 2004 and 2009, there was a sample of over half a million patients. These authors did not find any differences with respect to ventricular arrhythmia or cardiac-caused death among the subjects who received more than 40 mg/day and those that did not exceed 20 mg/day. They emphasised, in addition, that the data obtained were the same as those found in a similarly sized population treated with sertraline, a drug that has no alert hanging over it. In this article the authors questioned the need to maintain the alert on this antidepressant.

In normal clinical practice as far as dose and indication for escitalopram are concerned, there have only been 2 single cases communicated (''case reports'') of LQT and arrhythmia. The first of these[10] was a healthy 42-year-old female patient; this was a case observed in Taiwan. The QT returned to normal after drug treatment was stopped. The second case[11] was published in the USA. A 40-year-old female patient began to present fainting spells and falls after the fluoxetine that she was taking was replaced with 40 mg of citalopram twice a day. The authors believe that the patient had congenital LQTS that was ''unmasked'' by the citalopram given. Consequently, the 2 published cases of escitalopram-induced LQT in daily practice out of the millions of patients who have taken it in the entire world do not constitute a concern for the clinician, apart from the fact that the phenomenon is possible but highly improbable.

There are 2 mechanisms by which a drug induces non-congenital LQTS in an individual. One possibility is by the mutation of 1 of the genes that codify the proteins that regulate the opening of the potassium channel, while the other is that the drug itself interferes with 1 of these proteins. Although the latter option has been indicated as possibly responsible for this isolated case or for drug poisoning cases, the truth is that the experimental data do not support this at all.

The G protein activated inwardly rectifies the flow in potassium (K) channels (GIRK). This protein, also known as Kir3, is activated through various receptors attached to it; 4 subtypes have been identified. The drugs that inhibit it to a greater or lesser degree can reduce or slow down the output of intracellular K, lengthening repolarization at the level of the cardiac muscle. A preclinical study[12] carried out in Japan years ago established a type of ''ranking'' of antidepressant drugs that showed this capability. Although the subtype affected varied according to the drug, all the tricyclic antidepressants (imipramine, desipramine, amitriptyline, nortriptyline and clomipramine) were much stronger in inhibiting the K-channel regulating protein than citalopram. Maprotiline (tetracyclic) demonstrated activity similar to

imipramine and, with respect to the SSRIs, fluoxetine tripled the effect of citalopram. Fluvoxamine and bupropion did not seem to affect the activity of the K channels at all. The same Japanese group has recently published results[13] on the rest of the antidepressants. Sertraline (specifically) and, to a lesser degree, duloxetine and venlafaxine exert an inhibitory effect on these structures, while mianserin and mirtazapine have practically no effect on them. These authors do not make a direct transfer to clinical practice, given the preclinical and experimental nature of their work. However, they clearly show that the effect of antidepressants on ion flow can be related to therapeutic and secondary effects, principally on the heart and nervous system.

The cases described of LQT with citalopram were detected in subjects who had taken a mean of 140 mg in circumstances of intoxication,[7] 4 times the maximum recommended dose. Cases of ventricular arrhythmia or severe LQT have been found in terminal kidney patients or those with serious ionogram alterations, in contrast to those described in patients treated with tricyclics or haloperidol.

Even so, the possibility of inducing LQT exists with citalopram. However, it should be remembered that other drugs (like the rest of the SSRIs) have not been studied adequately and that the entire range of tricyclics are considered, literally, as drugs that prolong QT as a class effect.[14] Consequently, the alternatives to citalopram and escitalopram should be viewed with caution and with this perspective in mind.

Another consideration is that the cardiac toxicity of escitalopram is not very relevant in general. This was demonstrated in a recent randomized double blind controlled clinical trial[15] against a placebo published in the *JAMA*. Escitalopram significantly reduced the risk of mental stress-induced myocardial ischemia (MSIMI). No case of LQT was registered.

Finally, although the concept of the QT segment is accessible to any clinician, it should be remembered that the measurement of this parameter can vary with cardiac frequency. Consequently, the segment should be adjusted, which constitutes the QTc, or QT interval corrected for cardiac frequency.

The most sensible recommendations shared by a large part of the authors with respect to the indication for citalopram and escitalopram are as follows:

(1) Citalopram is reasonably safe at therapeutic doses. The possible increase in QTc is small and does not represent an increased risk of arrhythmia in healthy individuals.
(2) There is an association with QT with high/toxic levels in plasma.
(3) This drug should be avoided in patients with a personal or family history of sudden death or of having presented repetition syncope of unknown origin.
(4) An ECG should always be performed with any new drug begun as treatment after a certain age, as well as periodic ionogram monitoring (Na, K and Ca).
(5) If citalopram or escitalopram is substituted because of the appearance of syncope of unknown origin or of finding QTc prolongation, the new drug indicated should be monitored with regular ECGs, given the relevance of the idiosyncratic factor of the patient in the face of this type of toxicity. The following site associated with the American Medical Association (AMA) keeps an up-to-date list by risk groups about the capability of all drugs to prolong QT: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

At any rate, any temptation to change should involve a consideration of risks/benefits that continuing the treatment would represent for the vast majority of patients. If this alarm serves to improve our patients' safety, it will leave a positive ''residue''. In contrast, if it implies the substitution of treatment for, on occasions, another drug of greater risk (tricyclics or sertraline) or the reduction of the dose to a level below therapeutic doses, it can promote defensive medicine and ignoring clinical criteria at the moment of making decisions. No more depressive relapses should occur from this cause. The risk of suicide represented by a new relapse is, by far, a difference significantly higher than inducing a QT prolongation that might put the life of the patient in danger.

Ethical responsibilities

Protection of persons and animals. The authors declare that no experiments were carried out on human beings or animals for this research.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

Enrique Alvarez has received fees for carrying out teaching activities from various pharmaceutical companies including Eli Lilly, Lundbeck, Pfizer, Sanofi and Bristol-Myers. He has also participated as a local or national coordinator in clinical trials sponsored by these companies.

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References

1. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation. 1993;88:782–4.
2. FDA Drug Safety Communication. 2011, August 24. Available at: http://www.fda.gov/drugs/DrugsSafety/ucm269086.htm [accessed 11.01.12].
3. EMA Patient Health Protection. 2011, October 27. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/10/WC500117061.pdf [accessed 15.05.13].
4. FDA Drug Safety Comunication. 2012, March 28. Available at: http://www.fda.gov/Drugs/DrugsSafety/ucm297391.htm [accessed 28.03.13].

5. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: Part 1. J Psychosoc Nurs Ment Health Serv. 2011;49:13–6.
6. Rasmussen SL, Overø KF, Tanghøj P. Cardiac safety of citalopram: prospective trials and retrospective analyses. J Clin Psychopharmacol. 1999;19:407–15.
7. Van Gorp F, Whyte IM, Isbister GK. Clinical and ECG effects of escitalopram overdose. Ann Emerg Med. 2009;54:404–8.
8. 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;29:346.
9. Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. Am J Psychiatry. 2013;170:642–50.
10. Tseng PT, Lee Y, Lin YE, Lin PY. Low-dose escitalopram for 2 days associated with corrected QT interval prolongation in a middle-aged woman: a case report and literature review. Gen Hosp Psychiatry. 2012;34:210.e13–5.
11. Deshmukh A, Ulveling K, Alla V, Abuissa H, Airey K. Prolonged QTc interval and torsades de pointes induced by citalopram. Tex Heart Inst J. 2012;39:68–70.
12. Kobayashi T, Washiyama K, Ikeda K. Inhibition of G protein-activated inwardly rectifying K+ channels by various antidepressant drugs. Neuropsychopharmacology. 2004;29:1841–51.
13. Kobayashi T, Washiyama K, Ikeda K. Inhibition of G protein-activated inwardly rectifying K+ channels by different classes of antidepressants. PLoS ONE. 2011;6:e28208.
14. 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.
15. Jiang W, Velazquez EJ, Kuchibhatla M, Samad Z, Boyle SH, Kuhn C, et al. Effect of escitalopram on mental stress-induced myocardial ischemia: results of the REMIT trial. JAMA. 2013;309:2139–49.