Mort sobtada cardíaca per psicofàrmacs

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Universitat de Girona

Introducció

el Periódico
SOCIEDAD

PORTADA | INTERNACIONAL | POLÍTICA | ECONOMÍA | SOCIEDAD | BARCELONA | DEPORTES | OCIO Y CU

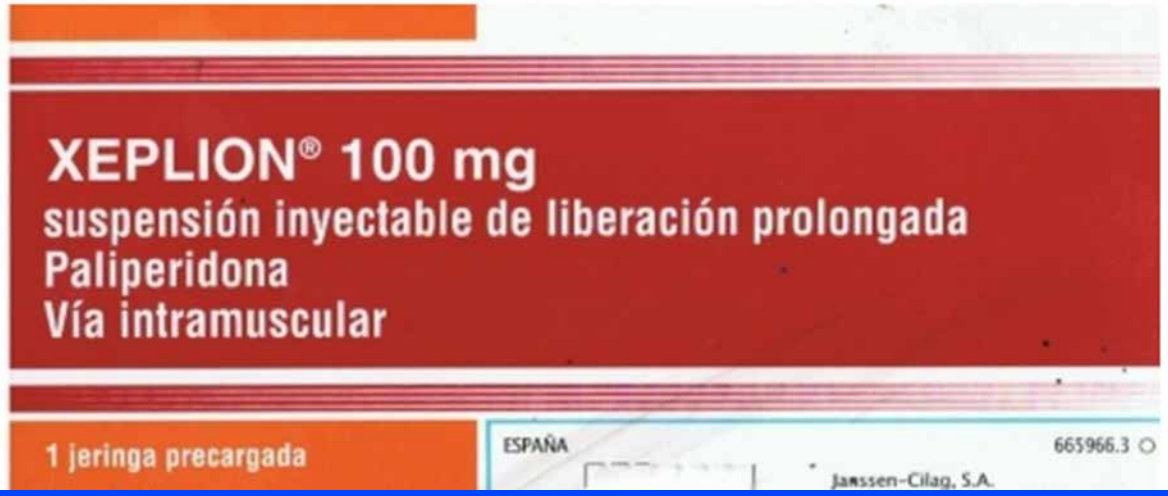
Castellers | Ciencia | Educación | Medio ambiente | Meteorología | Sanidad | Suce

+Personas | +Salud

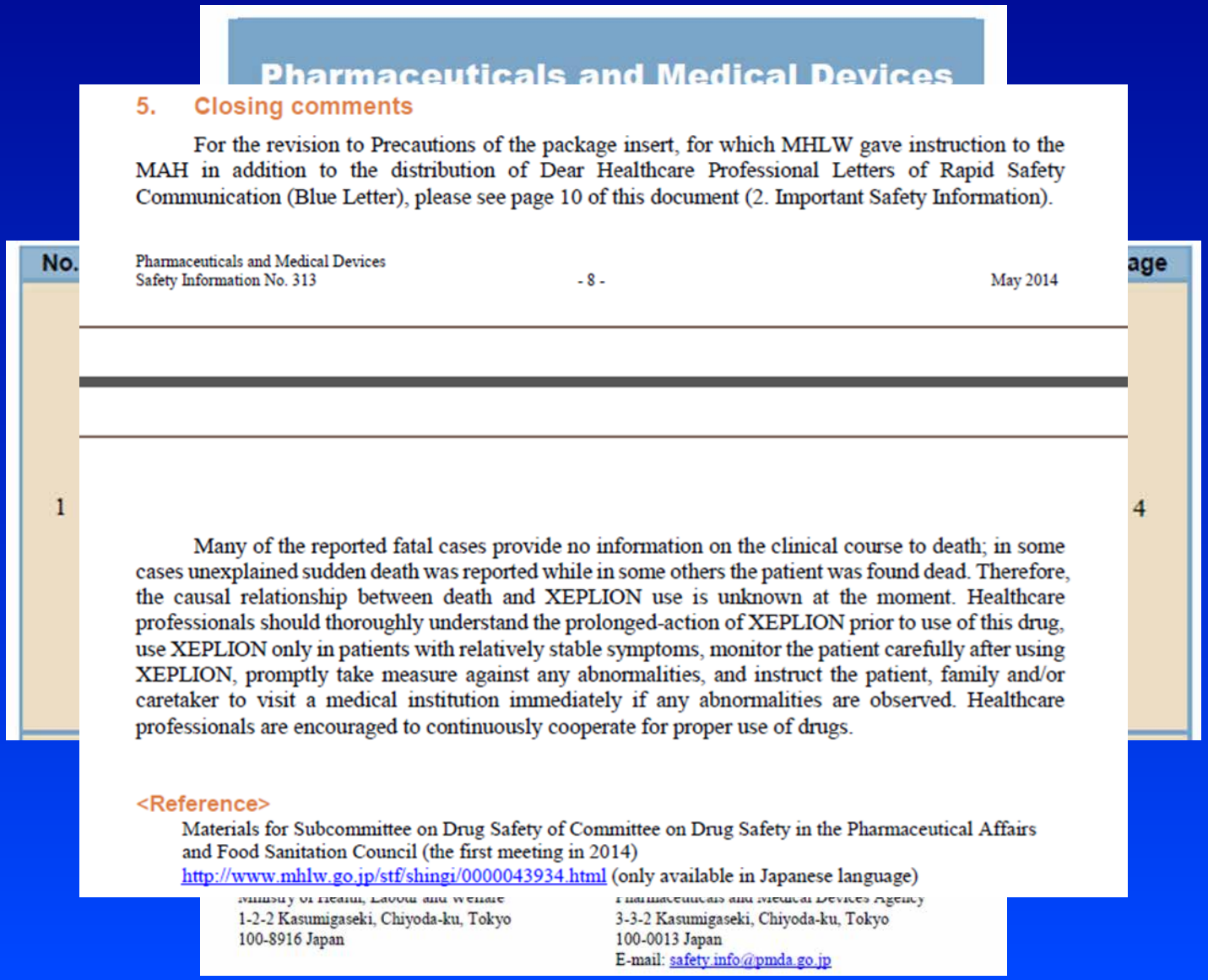
ALERTA SANITARIA

Al menos 17 personas mueren en Japón tras recibir inyecciones contra la esquizofrenia

- La posible causa de las muertes es el medicamento Xeplion, de la multinacional Johnson & Johnson, autorizado en 78 países incluido España



Introducció



Pharmaceuticals and Medical Devices

5. Closing comments

For the revision to Precautions of the package insert, for which MHLW gave instruction to the MAH in addition to the distribution of Dear Healthcare Professional Letters of Rapid Safety Communication (Blue Letter), please see page 10 of this document (2. Important Safety Information).

Many of the reported fatal cases provide no information on the clinical course to death; in some cases unexplained sudden death was reported while in some others the patient was found dead. Therefore, the causal relationship between death and XEPLION use is unknown at the moment. Healthcare professionals should thoroughly understand the prolonged-action of XEPLION prior to use of this drug, use XEPLION only in patients with relatively stable symptoms, monitor the patient carefully after using XEPLION, promptly take measure against any abnormalities, and instruct the patient, family and/or caretaker to visit a medical institution immediately if any abnormalities are observed. Healthcare professionals are encouraged to continuously cooperate for proper use of drugs.

<Reference>

Materials for Subcommittee on Drug Safety of Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the first meeting in 2014)
http://www.mhlw.go.jp/stf/shingi/0000043934.html (only available in Japanese language)

1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Mort sobtada

- Definició
- Causes de mort sobtada
  - Ictus
  - TEP
  - Mort sobtada cardíaca

Mort sobtada

- Causes de mort sobtada cardíaca
  - Miocardiopaties
  - Infart agut de miocardi
  - Mort sobtada no explicada

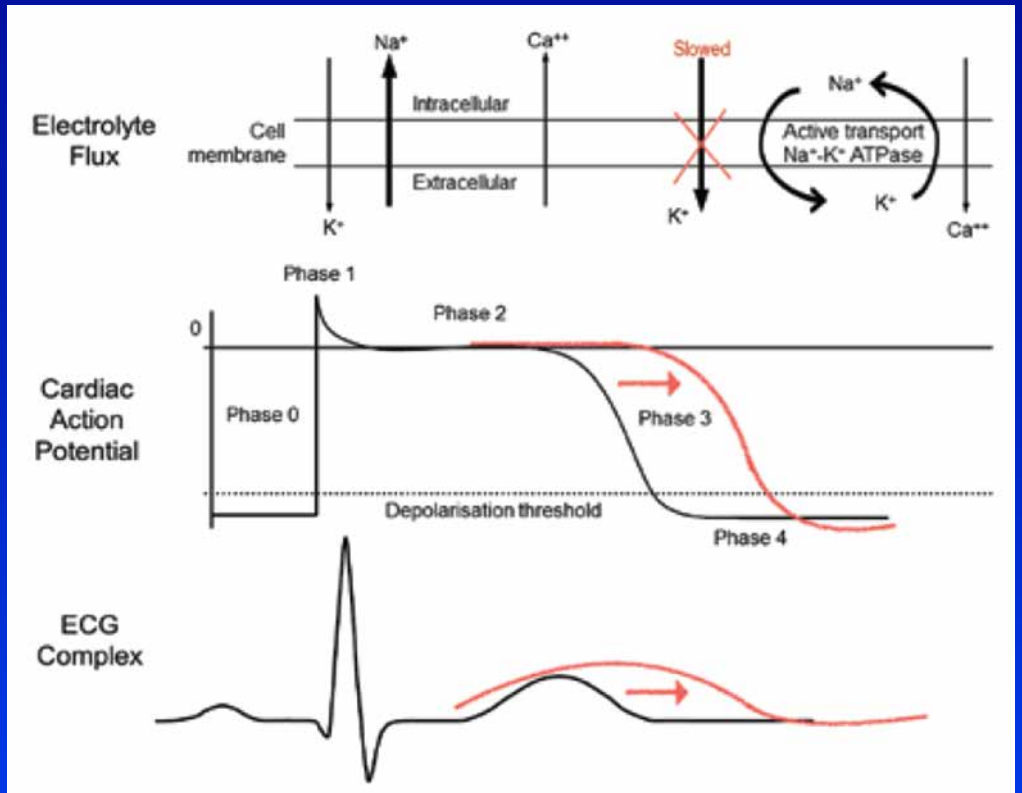
    15%

    Arítmies

Introducció

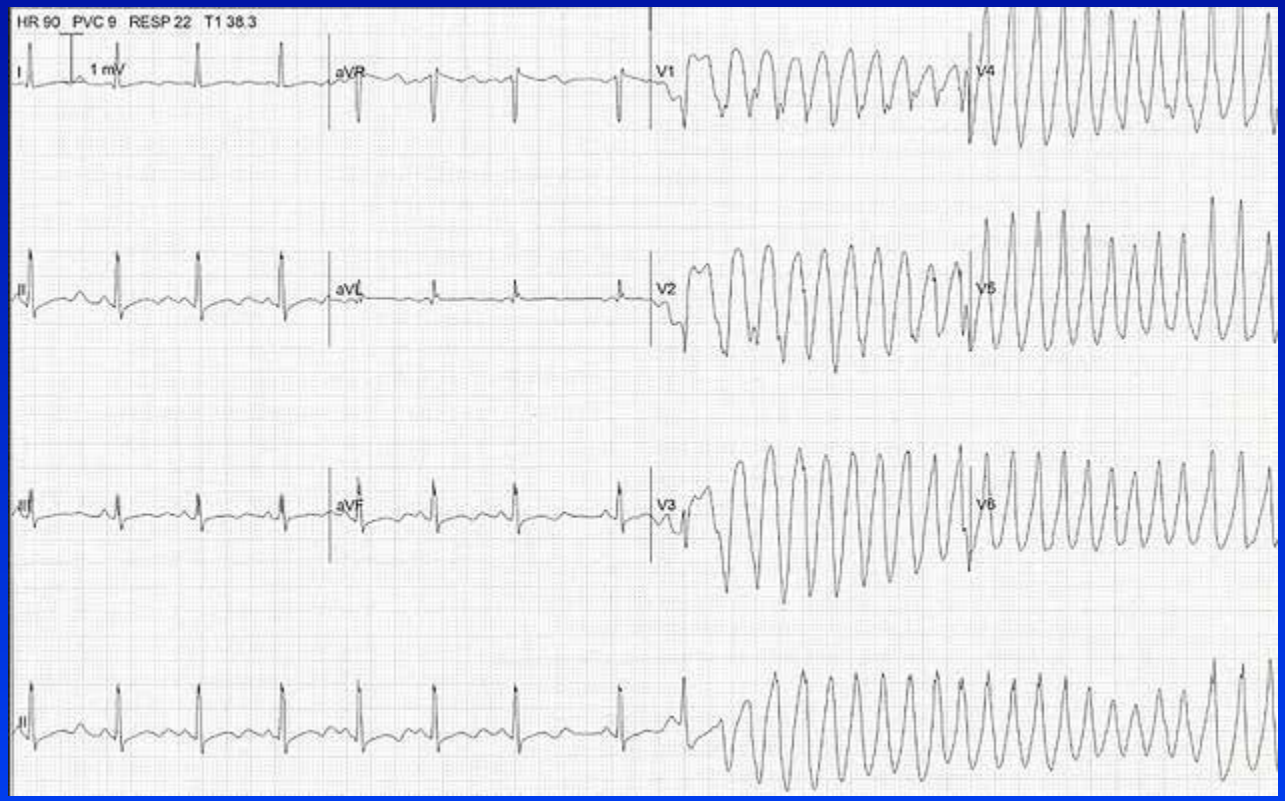
- Tipus d'arítmies
  - Alteracions de la repolarització
  - Bradicàrdia
  - Asistòlia

La despolarització cardíaca



phase 0	rapid depolarisation due to rapid sodium influx
phase 1	initial repolarisation due to potassium and chloride efflux
phase 2	the plateau where there is a balance of potassium efflux and calcium influx
phase 3	rapid repolarisation due to potassium efflux
phase 4	the resting membrane potential before the next depolarisation
———	indicates QT prolongation and its associated pathophysiology

La despolarització cardíaca



Alteracions de la repolarització

- Classificació segons el risc de causar arítimies ventriculars
  - Fàrmacs que causen *torsade de pointes*
  - Fàrmacs amb possible risc de *torsades de pointes*, bé a dosis altes o en pacients amb altres factors de risc
  - Fàrmacs que allarguen el QT

Alteracions de la repolarització

- Fàrmacs que causen TdP

Taula 1. Fàrmacs que poden causar *torsades de pointes*.

Antiarítmics. amiodarona, disopiramida, dofetilida, ibutilida, procaïnamida, quinidina, sotalol
Antihistamínics H1. astemizol, terfenadina
Antiinfecciosos. claritromicina, eritromicina, esparfloxacina, pentamidina
Antipalúdics. cloroquina, halofantrina
Antipsicòtics. clorpromazina, haloperidol, mesoridazina, pimozida, tioridazina
Procinètics. cisaprida, domperidona.
Opiacis. levacetilmetadol, metadona.
Altres. bepridil, droperidol, probucol, triòxid d'arseni

BFC 2010

Alteracions de la repolarització

- Fàrmacs amb possible risc de *torsades de pointes*, bé a dosis altes o en pacients amb altres factors de risc

Taula 2. Fàrmacs amb possible risc de *torsades de pointes*, bé a dosis altes o en pacients amb altres factors de risc.

Antianginosos. ranolazina
Antiarítmics. dronedarona, flecaïnida, mexiletina
Anticolinesteràsics. galantamina
Antidepressius. amitriptilina, citalopram, clomipramina, desipramina, doxetina, escitalopram, fluoxetina, imipramina, nortriptilina, paroxetina, protriptilina, sertralina, trazodona, trimipramina, venlafaxina
Antiemètics (setrons). dolasetron, granisetron, ondansetron
Antiepilèptics. felbamat, fosfenitoïna
Antifúngics. fluconazol, itraconazol, ketoconazol, voriconazol
Antihipertensius. isradipina, moexipril+hidroclorotiazida, nicardipina
Antihistamínics H1. difenhidramina
Antiinfecciosos. amantadina, azitromicina, atazanavir, ciprofloxacina, foscarnet, gatifloxacina, gemifloxacina, levofloxacina, moxifloxacina, ofloxacina, ritonavir, saquinavir, roxitromicina, trimetoprim-sulfametoxazol, telitromicina
Antineoplàstics. lapatinib, nilotinib, sunitinib
Antipsicòtics. clozapina, paliperidona, quetiapina, risperidona, sertindol, ziprasidona
Atropínics en la incontinència urinària. solifenacina
Bloquejadors α_1 per a la hipertròfia benigna de pròstata. alfuzosina
Diürètics. indapamida
Sedants. hidrat de cloral
Altres. apomorfina, liti, octreòtida, oxitocina, perflutrèn (agent de contrast), tacrolimus, tamoxifèn, tizanidina, vardenafil

BFC 2010

Alteracions de la repolarització

- Pacients amb altres factors de risc

- Uso de fármacos que prolongan el QT.
  - Interacciones de medicamentos (uso concomitante de más de un medicamento que prolonga el intervalo QT o uso concomitante con inhibidores del metabolismo).
  - Dosis altas, sobredosis, infusión rápida de medicamentos IV.
- Alteraciones electrolíticas (hipopotasemia, hipomagnesemia, hipocalcemia).
- Sexo femenino.
- Edad avanzada.
- Bradicardia.
- Cardioversión reciente de fibrilación auricular a ritmo sinusal.
- Enfermedad cardiovascular (ICC, IAM previo, HVI, ictus...).
- Insuficiencia renal o hepática.
- Hipertiroidismo/hipotiroidismo.
- Intervalo QT prolongado basal.
- Historia familiar de intervalo QT largo.

Alteracions de la repolarització

- Altres factors de risc

Taula 3. Fàrmacs que poden produir hipopotassèmia.

diürètics de nansa, tiazídics, acetazolamida
amfotericina B (per via intravenosa)
antibiòtics (gentamicina)
laxants estimulants
immunosupressors (sirolimus, temsirolimus, leflunomida)
corticoides (tetracosàctid)
estimulants β-adrenèrgics (bambuterol, formoterol, salbutamol, salmeterol, terbutalina, ritodrina)
broncodilatadors (teofil·lina)
insulina
regalèssia

Taula 4. Fàrmacs bradicarditzants

Antianginosos. ivabradina, ranolazina, bepridil
Antiarítmics. Classe I (cibenzolina, disopiramida, flecaïnida, hidroxiquinidina, lidocaïna, mexiletina, propafenona, quinidina); classe III (amiodarona, dofetilida, ibutilida, sotalol)
Anticolinesteràsics. donepezil, galantamina, rivastigmina
Antiepilèptics. fosfenitoïna
Antihipertensius. clonidina, moxonidina, metildopa, guanfacina, rilmenidina, reserpina
Antipalúdics. mefloquina
Bloquejadors β-adrenèrgics
Bloquejadors dels canals de calci bradicarditzants. diltiazem, verapamil
Colinèrgics. acetilcolina, pilocarpina
Ergòtics. dihidroergotoxina
Inhibidors de la colinesterasa (miastènia). ambenonium, neostigmina, piridostigmina
Opiacis. metadona, fentanil
Altres. adenosina, aprepitant, digoxina, liti, talidomida

BFC 2010

Alteracions de la repolarització

- Psicofàrmacs que alteren la repolarització

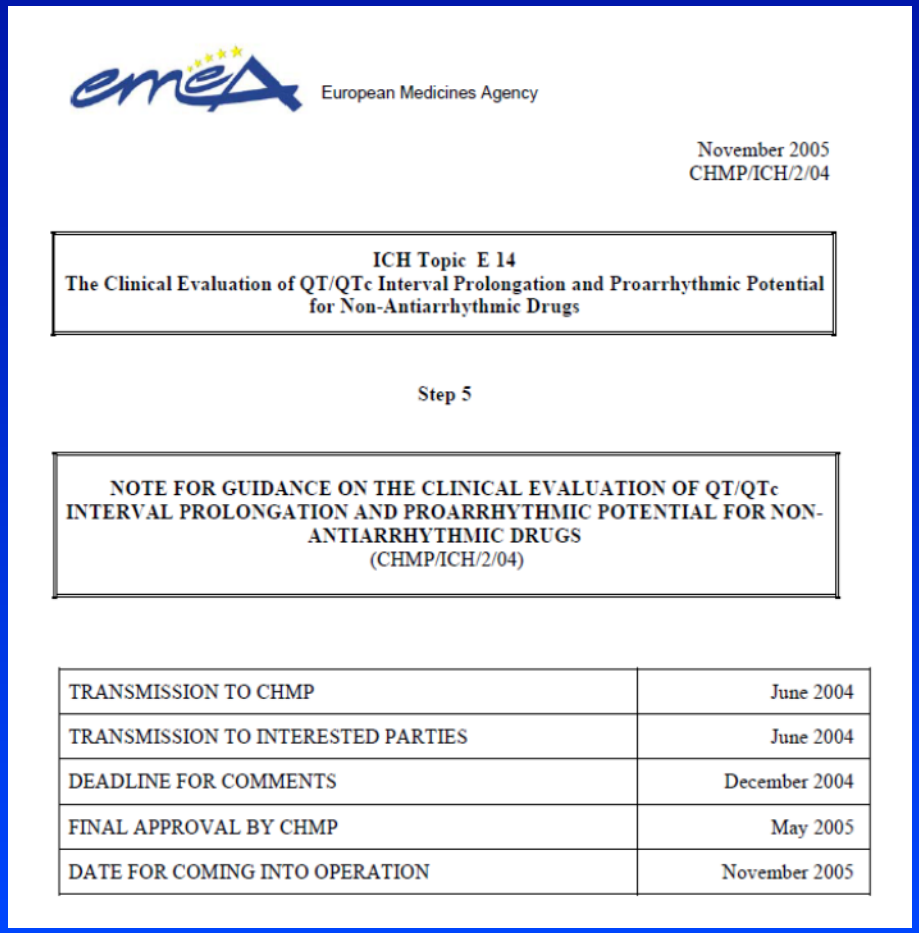
Antidepresivos		
Amitriptilina	■	Riesgo condicional. Riesgo de TdP con sobredosis
Citalopram	✖	Riesgo de TdP
Clomipramina	■	Riesgo condicional. Riesgo de TdP con sobredosis
Doxepina	■	Riesgo condicional
Escitalopram	✖	Riesgo de TdP
Fluoxetina	■	Riesgo condicional
Imipramina	■	Riesgo condicional. Riesgo de TdP con sobredosis
Maprotilina*		
Mirtazapina	◆	Posible riesgo
Nortriptilina	■	Riesgo condicional
Paroxetina	■	Riesgo condicional
Sertralina	■	Riesgo condicional
Trazodona	■	Riesgo condicional
Trimipramina	■	Riesgo condicional
Venlafaxina	◆	Posible riesgo

Antipsicóticos		
Amisulprida	■	Riesgo condicional. Riesgo de TdP con sobredosis
Clorpromazina	✖	Riesgo de TdP
Clozapina	◆	Posible riesgo
Droperidol	✖	Riesgo de TdP
Haloperidol	✖	Riesgo de TdP con vía IV o dosis excesiva
Litio	◆	Posible riesgo
Olanzapina	◆	Posible riesgo
Paliperidona	◆	Posible riesgo
Pimozida	✖	Riesgo de TdP
Quetiapina	◆	Posible riesgo
Risperidona	◆	Posible riesgo
Sertindol	◆	Posible riesgo
Ziprasidona	◆	Posible riesgo

INFAC 2014

Alteracions de la repolarització

- Accions regulatòries



European Medicines Agency

November 2005
CHMP/ICH/2/04

ICH Topic E 14
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Step 5

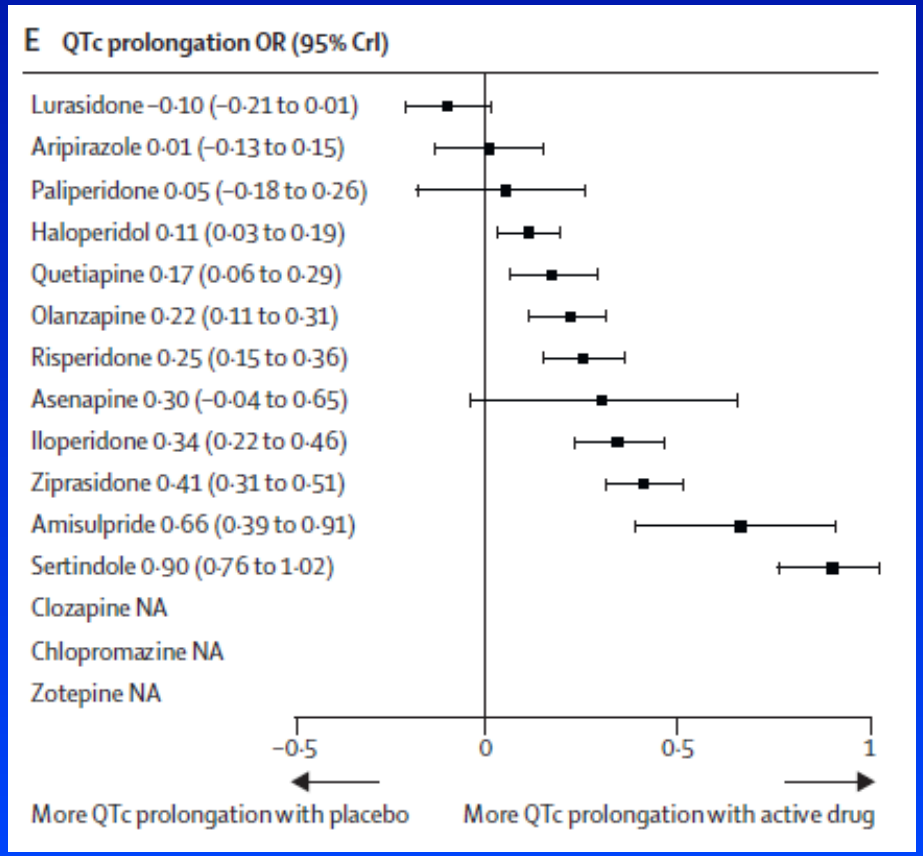
NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
(CHMP/ICH/2/04)

TRANSMISSION TO CHMP	June 2004
TRANSMISSION TO INTERESTED PARTIES	June 2004
DEADLINE FOR COMMENTS	December 2004
FINAL APPROVAL BY CHMP	May 2005
DATE FOR COMING INTO OPERATION	November 2005

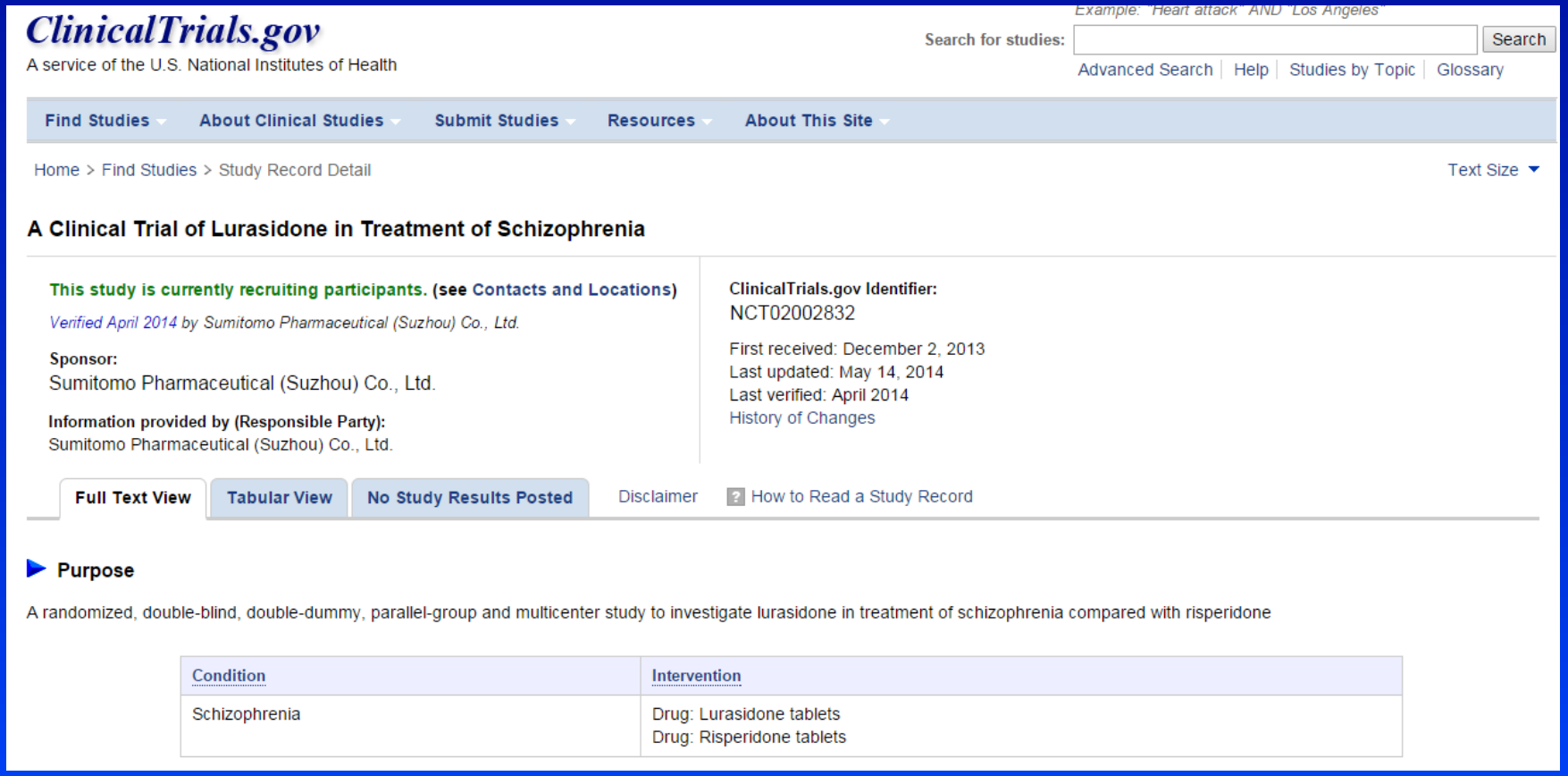
EMA 2005

Alteracions de la repolarització

- Accions regulatòries



Validesa dels resultats dels ACA



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail
Text Size

A Clinical Trial of Lurasidone in Treatment of Schizophrenia

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2014 by Sumitomo Pharmaceutical (Suzhou) Co., Ltd.

Sponsor:
Sumitomo Pharmaceutical (Suzhou) Co., Ltd.

Information provided by (Responsible Party):
Sumitomo Pharmaceutical (Suzhou) Co., Ltd.

ClinicalTrials.gov Identifier:
NCT02002832

First received: December 2, 2013
Last updated: May 14, 2014
Last verified: April 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

A randomized, double-blind, double-dummy, parallel-group and multicenter study to investigate lurasidone in treatment of schizophrenia compared with risperidone

Condition	Intervention
Schizophrenia	Drug: Lurasidone tablets Drug: Risperidone tablets

Validesa dels resultats dels ACA

Exclusion Criteria:

1. Subjects are pregnant (positive pregnancy test at screening) or are breast-feeding or are planning pregnancy for the duration of the study.
2. Subjects currently have a clinically significant neurological, metabolic (including type I diabetes), hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal and/or urological disorder. Subjects with human immunodeficiency virus (HIV) seropositivity (or history of seropositivity) will be excluded.
3. Subjects have acute or chronic hepatitis or severe hepatic impairment, or serum alanine transaminase (ALT) or aspartic transaminase (AST) level ≥3-fold upper limit of normal.
4. Subjects' estimated creatinine clearance is <30 mL/min, where creatinine clearance=Males: (140 - Age) x Weight (kg)/serum creatinine (mg/dL) x 72;Females: 0.85 x (140 - Age) x Weight (kg)/serum creatinine (mg/dL) x 72.
5. Subjects have a history of stomach or intestinal surgery or any other condition that could interfere with absorption, distribution, metabolism, or excretion of medications.
6. Subjects have a history of malignancy (including benign pituitary tumor).
7. Subjects have evidence of any chronic organic diseases of the CNS (other than schizophrenia), such as tumors related to the CNS, inflammation related to the CNS, active seizure disorder, vascular disorder, Parkinson's disease, Alzheimer's disease, or other forms of dementia, myasthenia gravis, or other degenerative processes. Subjects have a medical history of mental retardation or persistent neurological symptoms resulting from serious head injury.
8. Subjects have a medical history of neuroleptic malignant syndrome.
9. Subjects have evidence of severe tardive dyskinesia, severe dystonia or any other severe movement disorder.
10. Subjects are considered by the investigator to be at imminent risk of suicide or self-mutilation risks or other relevant characteristics.

Validesa dels resultats dels ACA

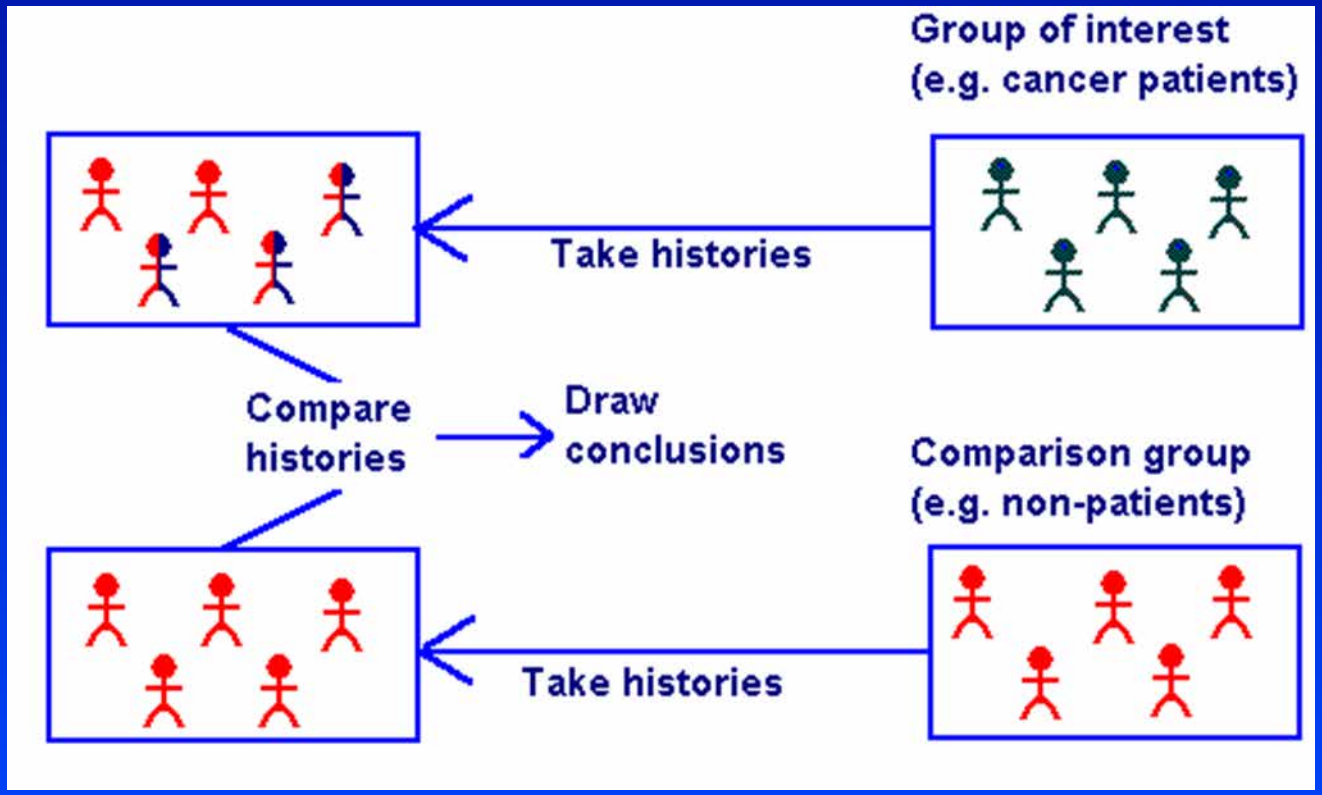
11. Subjects are alcohol abuse or alcohol dependence, or have a history of drug abuse including caffeine or nicotine abuse/dependence within 6 months before screening.
12. Subjects have a history of macular or retinochrome disorders.
13. Subjects have an HbA1c level of >7.0 % at Screening.
14. Subjects have long QT syndrome or require treatment with a drug which treats arrhythmia.
15. Subjects have poor peripheral venous condition unsuitable for injection or blood collection.
16. Subjects have a history of hypersensitivity to more than 2 distinct chemical classes of drug (e.g., sulfas, anti-convulsant and penicillins).
17. Subjects are allergic to risperidone or have a risperidone allergic history.
18. Subjects have used risperidone, long-acting risperidone, paliperidone or paliperidone palmitate within 1 month before screening, and/or experienced poor therapeutic effect or intolerance with those drugs.
19. Subjects are resistant to neuroleptic treatment, defined as failure to respond to 2 or more marketed antipsychotic agents from 2 different classes, given at an adequate dose for at least 8 weeks over the last one year.
20. Subjects have received long-acting neuroleptics and the interval within 6 weeks before informed consent.
21. Subjects have a history of treatment with clozapine for refractory psychosis and/or have been treated with clozapine within 4 months before informed consent.
22. Subjects have received fluoxetine hydrochloride, or monoamine oxidase (MAO) inhibitor within 2 weeks prior to informed consent.

Validesa dels resultats dels ACA

23. Subjects require treatment with any potent cytochrome P3A4 (CYP3A4) inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin) during the study (excluding dermatological drugs for topical use).
24. Subjects require treatment with a drug which prolongs QTc interval.
25. Subjects have received electric shock therapy within 3 months prior to informed consent.
26. Subjects demonstrate a decrease (improvement) of >20% in the PANSS score between the Screening and Baseline visits, or the PANSS score fall below 70 at Baseline. Note: The PANSS total score percentage change will be defined as (Baseline value -Screening value) X 100 / (Screening value - 30).
27. Subjects participated in other lurasidone study before.
28. Subjects have been screened or washed out previously more than twice for this study.
29. Subjects are participating or participated in other clinical studies including marketed drugs or medical devices within 30 days before signing the informed consent form.
30. Subjects are currently undergoing or will receive the treatment with epinephrine.
31. Subjects have a history of water intoxication or paralytic ileus.
32. Subjcets who are considered ineligible for the study by investigator.

Estudis observacionals

- Estudi de casos i controls



Estudis observacionals

- Problemes amb els estudis de casos i controls
  - Manca de registre de la mort en les bases de dades
  - Causa de la mort
  - Estudis forènsics
  - Interaccions i factors precipitants
  - Sèries de casos

Recomanacions

- Evitar fàrmacs que allarguin QT
- Dosis baixes que siguin eficaces
- Vigilar interaccions
- Realització ECG

  - No sistemàticament
  - Fàrmacs amb risc de TdP
  - Fàrmacs amb risc potencial de TdP administrats a pacients d'alt risc

www.azcert.org

Recomanacions

- Càlcul del QT

Table 2 **Step by step approach for using the QT nomogram to determine if a QT interval is abnormal** [1]

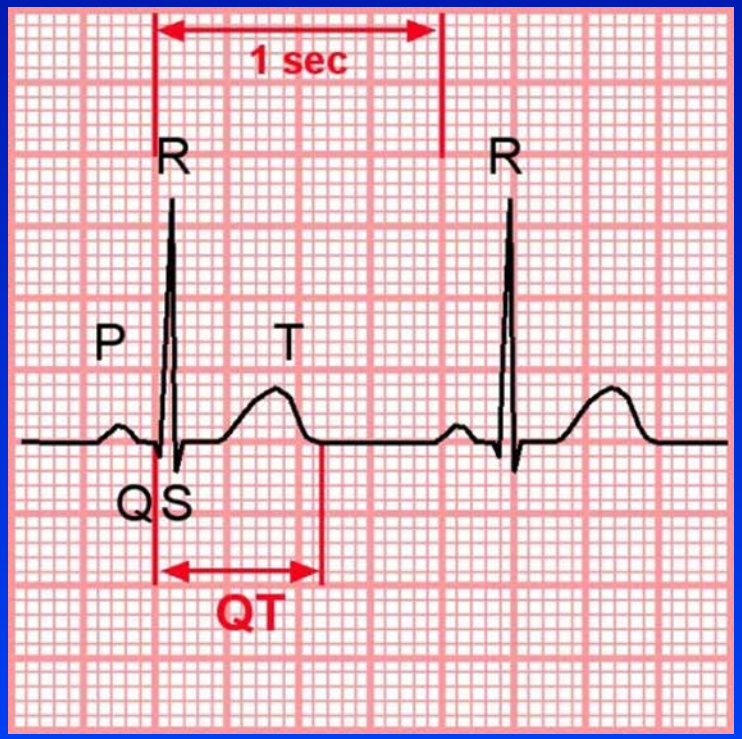
Steps	Approach
Obtain ECG	The QT interval length is manually measured in 6 leads on the ECG, usually: • 3 limb leads: I, II and aVF • 3 chest leads: V2, V4 and V6
Measure the absolute QT interval	The QT interval is manually measured from the start of the Q wave until the T wave returns to baseline On a standard ECG at 25 mm per second this is best done by counting the number of small squares • 5 small squares = 200 milliseconds • 8 small squares = 320 milliseconds Do not use the ECG automated readout or QTc
Calculate the median QT	The median is the middle number of all 6 measured QT intervals when arranged in numerical order If there are 2 middle numbers, e.g. position 3 and 4, then the average of these 2 measurements is the median
Determine heart rate	The heart rate is the average measurement derived from the RR interval on the 12 lead ECG and is most accurate when read from an automated ECG
Plot on QT nomogram	The median QT length is then plotted against the heart rate on the QT nomogram (Fig. 4). If the QT–heart rate pair is above the line on the nomogram it is a prolonged QT and there is an increased risk of torsades de pointes.

RR the distance from one R wave to the next R wave Modified from reference 1

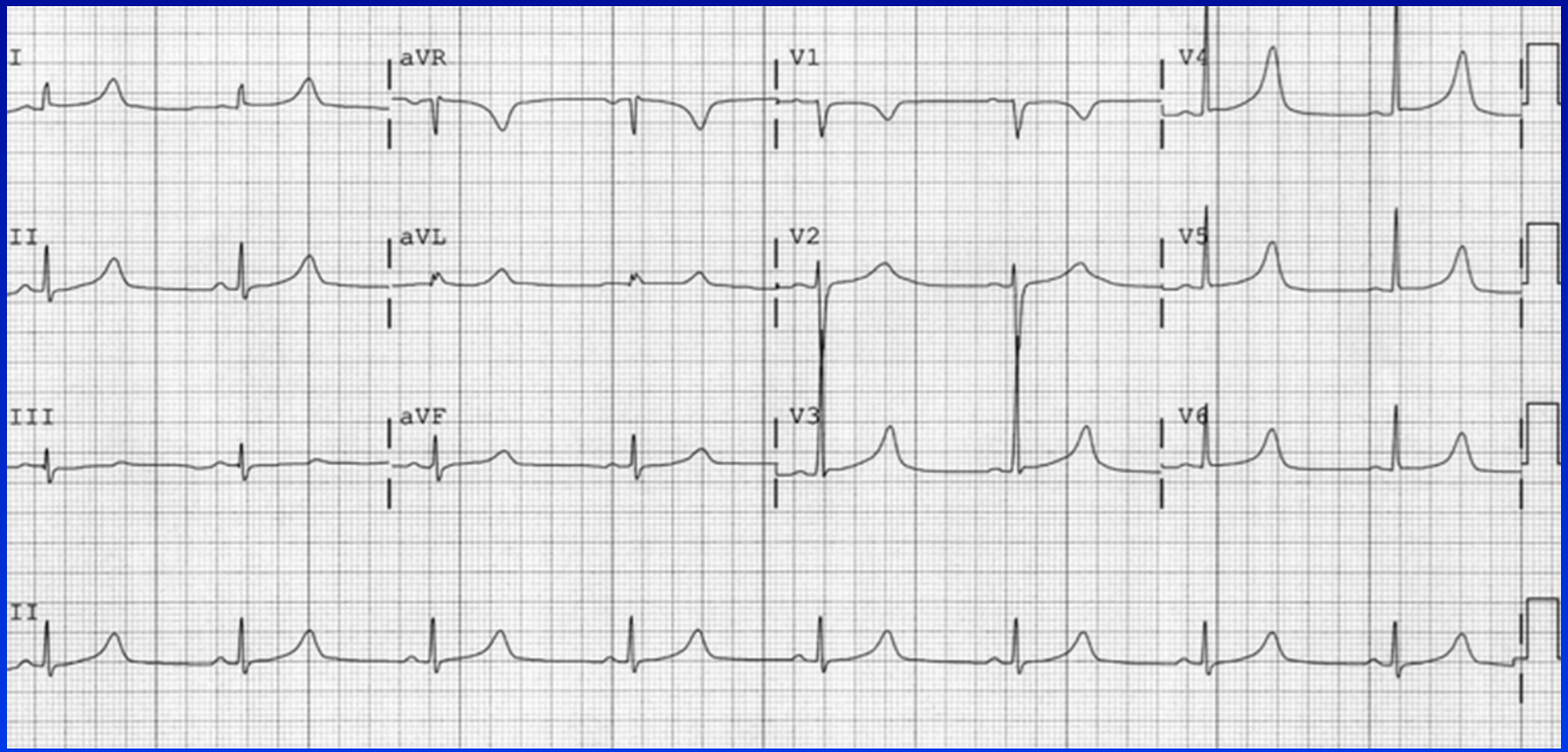
Isbister 2015

Recomanacions

- Càlcul del QT

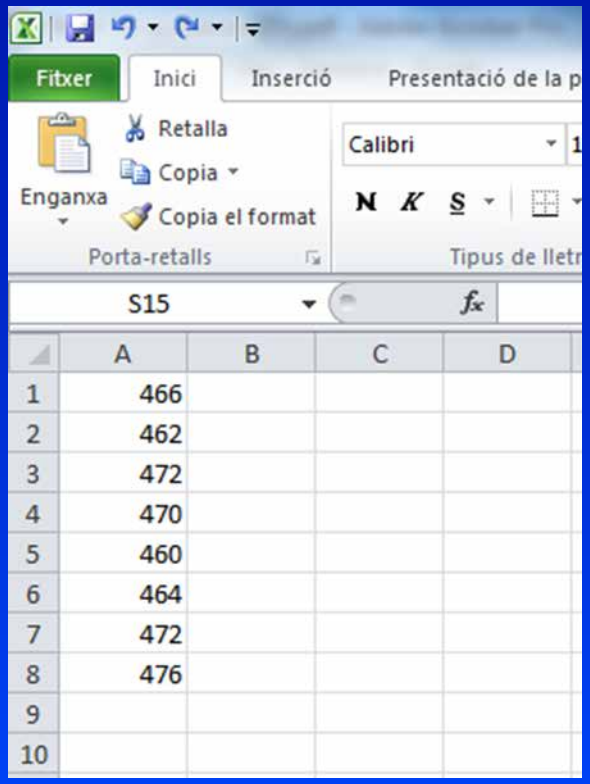


Recomanacions



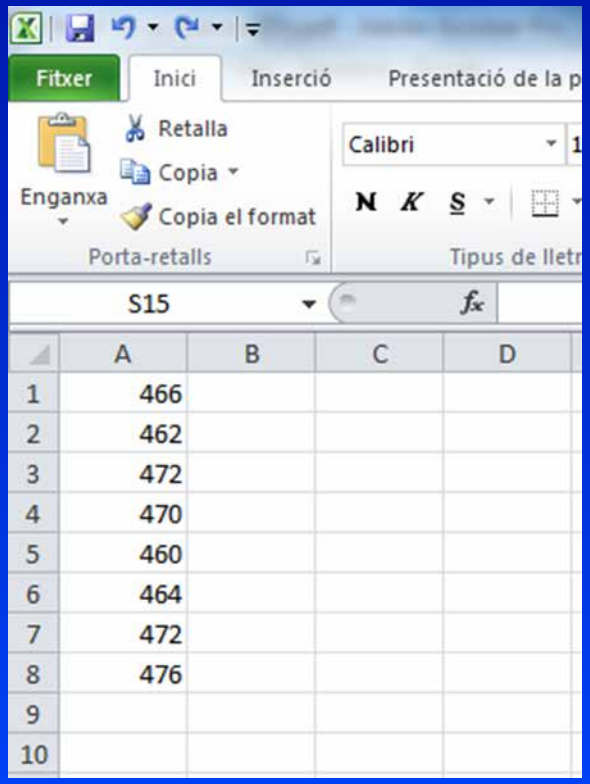
Recomanacions

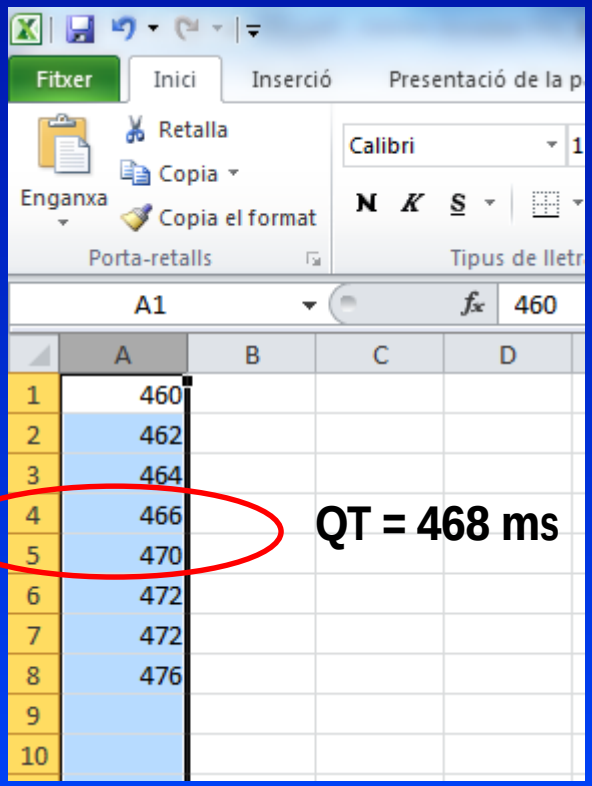
- Càlcul del QT



Recomanacions

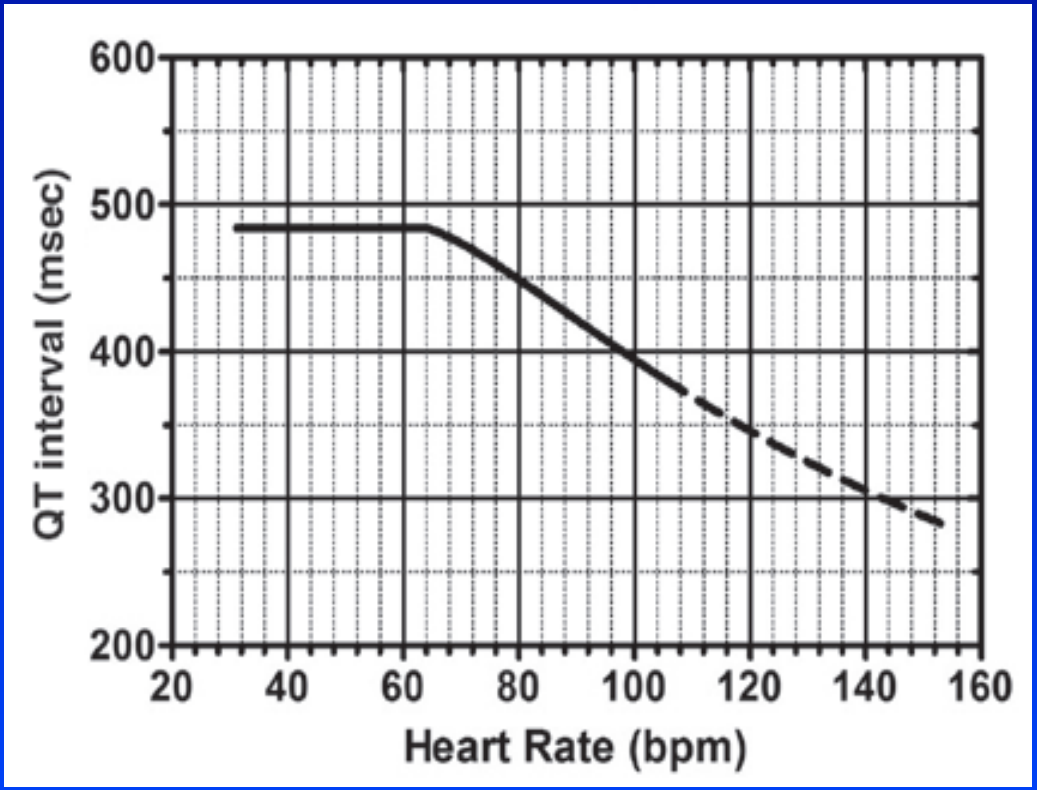
- Càlcul del QT





Recomanacions

- Càlcul del QT



Conclusions

- L'**allargament del QT** és un efecte indesitjat **freqüent** però les **arrítmies ventriculars** probablement són **rares**
- La majoria de fàrmacs que allarguen el QT provoquen arrítmies ventriculars quan **concorren altres circumstàncies aritmogèniques**
- La **informació** que disposem sobre els efectes indesitjats aritmogènics dels fàrmacs és **escassa**
- Existeixen mesures senzilles per **minimitzar els risc** aritmogènic dels medicaments

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