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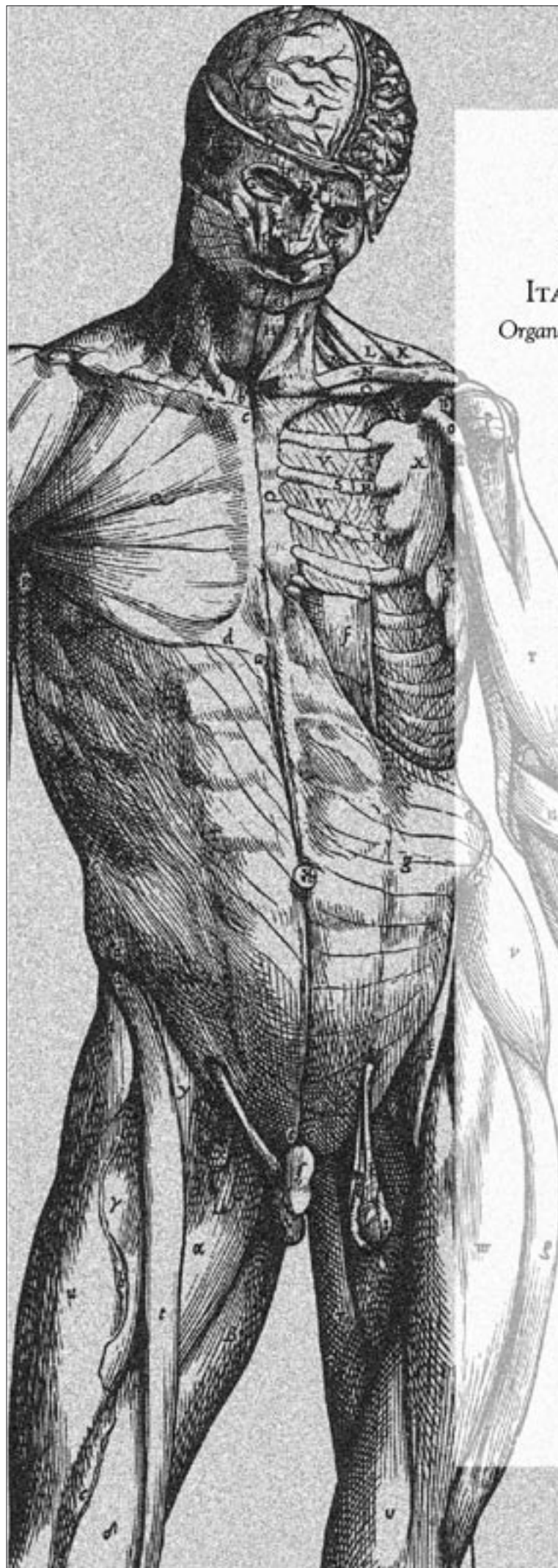
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QT Interval

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Summary

The electrocardiogram records the electrical activity of the heart, the depolarization and repolarization of the atria and ventricles. Deflections are all shown by the single features of the electrocardiogram: the P wave, the QRS complex, the T wave, the U wave, the PR interval and the QT. The QT interval represents the entire electrical activity of the left ventricle: it begins with the onset of ventricular depolarization (start of the Q wave) and is completed when ventricular repolarization ends (at the end of the T wave). Measurement of the QT interval is important because of the useful information it provides on the electrical activity of the heart; the length of the interval depends on various pathophysiological conditions, changes in electrolyte concentration, and the pharmacological action of toxic substances.

Key Words: ECG; QT Interval; QT measurement

1. Introduction

An electrocardiogram allow the measurement of the electrical activity of the heart: atrial depolarization and repolarization are consistent with contraction of the atria, whilst ventricular depolarization and repolarization correspond to contraction of the ventricles. These phenomena are followed by a recovery phase coinciding with the isoelectric line.

The single deflections of an electrocardiogram can be defined as follows:

- P wave: deflection consistent with atrial depolarization
- QRS complex: corresponding to ventricular depolarization comprising four types of waves:
 - Q wave: an initial negative deflection preceding the first positive deflection
 - R wave: first positive deflection
 - S wave: first negative deflection subsequent to an R wave
 - QS wave: a purely negative deflection unaccompanied by a positive wave
- T wave: deflection corresponding to ventricular repolarization

- U wave: deflection occurring after a T wave and elicited by repolarization of papillary muscles

The main intervals are:

- PR interval: corresponding to the duration of atrio-ventricular conduction
- QT interval: interval between the onset of ventricular depolarization (beginning of Q wave) and termination of ventricular repolarization (end of T wave).

The QT interval accounts for the entire electrical cycle of the left ventricle and is utilized in measuring the duration of ventricular repolarization.

The onset of ventricular depolarization is readily discernible, as it occurs concomitantly with the first QRS deflection. The onset of repolarization, on the other hand, is less easily definable, due to the fact that not all ventricular cells are repolarized simultaneously; so it is the electric systole, the QT interval, that is usually defined.

The electrocardiographic measurement of the QT interval is a procedure of major importance, as it provides information on the heart's electrical activity, which may be altered by a wide variety of physiopathological conditions, including electrolytic imbalance, and the action of drugs or toxic compounds on the heart. Conduction

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Figure 1. QTc according to age and gender

Age and gender	1-15 years	Males	Females
Normal	<440 msec	<430 msec	<450 msec

abnormalities, including bundle branch blocks and pre-excitation, may produce repolarization alterations capable of influencing QT interval.

2. Measurement of the QT interval

The QT interval should be calculated from the initial deflection of the QRS complex. Incorrect calculations may be made when measuring QT at a single lead, as the initial QRS vectors may be located perpendicularly to the lead line, so abolishing the initial deflection and leading to an incorrect interpretation. Several authors suggest the advisability of obtaining steady measurements from leads V5 and V6, but the best way to achieve reliable results is to calculate QT using data obtained from all 12 leads, taking the longest measurement obtained as the final outcome [1, 3].

Distinguishing between T and U waves may prove to be a hard task, especially when the latter are pronounced. It may likewise be complicated to discriminate between a U wave situated close to a T wave of the type just mentioned, and a bifid T wave. When taking into account an entire bifid T wave, the resulting QT will be longer than that obtained measuring T as proximal and U as distal deflection. In view of the fact that the U wave is particularly evident in precordial leads, when a bifid T wave is observed across all leads it is feasible to assume that the wave is truly bifid and therefore calculate QT on the basis of the two deflections.

It should be stressed that some electrocardiographs are capable of calculating the QT interval automatically. The measurements so obtained are, however, thought to be unreliable; in more complex cases, such as those described previously, they may even provide totally incorrect readings.

The QT interval measured by single ECG leads may vary as a function of different recovery times recorded for specific heart regions: the difference between a prolonged and a shorter QT interval is commonly known as dispersion of the QT interval (QTd), and is applied in assessing disparity in ventricular repolarization. Values ranging between 20 and 40 msec are considered normal. An increased QTd has been reported in various heart disorders, including congestive heart failure, hypertrophic cardiomyopathy, prolapse of the mitral valve and ischaemic heart disease.

3. QT and heart rate

The QT interval is closely dependent on the heart rate, being shorter at a fast heart rate and prolonged when the heart rate is lower. Bazett's formula is applied in measuring Qt in relation to heart rate (QTc or corrected QT): [2]

$$QTc = QT / \sqrt{R-R \text{ interval}}$$

On assuming a duration of one second for the R-R interval, corresponding to a heart rate of 60 beats per minute (b/min), R-R is therefore equal to 1 and QTc identical in length to QT.

Mean normal QTc values of 0.430 sec are obtained for adult males; higher values are indicative of a pathological condition. In adult females normal values correspond to 0.450 sec. In pre-pubescent subjects a normal value of 0.440 sec is obtained, irrespective of gender (Table 1).

It should, however, be emphasized that the QT interval does not vary simultaneously with changes in heart rate, requiring a time-lag of 1-2 minutes to adapt, and varying on the basis of individual response. An incorrect measurement may be obtained if QT is assessed immediately after a change in heart rate.

4. Prolonged QT interval

Numerous conditions may underlie a prolonged QT interval – some acquired and others correlated with specific chromosomal alterations of a congenital nature.

Disorders featuring a congenital prolonged QT interval are classified in a group of disorders known as the Congenital long QT syndrome, comprising:

- an autosomal recessive disorder, the Jervell and Lange-Nielsen Syndrome, associated with deafness [6]
- an autosomal dominant disorder, the Romano-Ward Syndrome, not associated with hearing deficits [10, 15].

Numerous forms of long-QT syndrome have been identified, each featuring a specific physiognomy with regard to ion currents involved and mutated genes.

The most common forms taken by congenital long QT syndrome are LQTs1-LQTs2-LQTs3, accounting for 95% of forms, all associated with different genes.

LQTs1 is the most frequently expressed form, found in 70% of arrhythmias occurring during physical exertion.

In LQTs2 arrhythmias are more frequently associated

with an emotional cause.

In the LQTs3 form, 55% of arrhythmias take place during sleep. LQTs3 is increasingly associated with a fatal outcome.

From an electrocardiographic viewpoint, diagnostic screening is provided by ECG evidence of a prolonged QT, i.e. >450 msec in males and >460 msec in females. A diagnosis of LQTS in subjects displaying a prolonged QT at surface ECG is dependent on a wide array of clinical and instrumental parameters, as listed in Table 2 [11].

In this table a score of 1 denotes a subject at low risk of LQTS, a score of 2 or 3 indicates an intermediate

Clinical and instrumental characteristics	Score
QTc (msec)	
≥480	3
460-470	2
450 (nei maschi)	1
VT torsades de pointes type	2
T wave alternans positive	1
T wave with engraver in three derivations	1
Relative for age bradycardia	0.5
Clinical history	
Stress syncope	2
Syncope without stress	1
Congenital deafness	0.5
Family history	
LQTs found	1
Sudden death before 30 years old	0.5

probability of presenting LQTS and a score of 4 denotes a high risk of LQTS.

Patients affected by LQTS frequently remain asymptomatic throughout their entire lifetime, with sudden death occurring during the first episode ever to occur in 12% of cases.

Subjects featuring a past cardiac arrest should be treated by means of a defibrillator implant, whilst other patients may be given a prescription for drug treatments. The means of treatment varies according to the risk of arrhythmias.

5. Acquired prolonged QT

A prolonged QT interval may be the result of a genetic alteration of ion channels, whether drug-related or caused by an electrolyte imbalance.

5.1 Drugs

Many different drugs are capable of prolonging the QT interval. In particular, the effects produced by class I and class III anti-arrhythmic drugs and drugs acting on the central nervous system should be carefully noted. In some cases drugs may act on a predisposed substrate, delatentizing previously undetected ion current anomalies. An increased risk of fatal arrhythmias during the administration of anti-arrhythmic drugs inducing a prolonged QT interval is limited to the early stage of treatment. Administration of these drugs should therefore be initiated in a hospital setting, a precaution that has proved to be extremely cost-effective [12].

Table 3 lists drugs capable of prolonging the QT interval.

Haloperidol	Neuroleptic
Amiodarone	Antiarrhythmic
Amitriptyline	Antidepressant
Ampicillin	Antibiotic
Azithromycin	Antibiotic
Chlorpromazine	Neuroleptic
Clomipramine	Antidepressant
Domperidone	Antiemetic
Erythromycin	Antibiotic
Flecainide	Antiarrhythmic
Fluoxetine	Antidepressant
Imipramine	Antidepressant
Indapamide	Diuretic
Ketoconazole	Antifungal
Metoclopramide	Antiemetic
Nortriptyline	Antidepressant
Procainamide	Antiarrhythmic
Sotalol	Antiarrhythmic
Tamoxifen	Anticancer
Trimethoprim - Sulfamethoxazole	Antimicrobial
Citalopram	Antidepressant
Droperidol	Neuroleptic
Felbamate	Anti epileptic
Levomepromazine	Neuroleptic
Lithium	Mood stabilizer
Methadone	Opiate
Olanzapine	Antipsychotic
Risperidone	Antipsychotic

Table 3. Drugs capable of prolonging the QT interval

Sertraline	Antidepressant
Venlafaxine	Antidepressant
Tioridazine	Neuroleptic
Tizanidine	Muscle relaxation

5.2 Electrolyte alterations

Hypokalaemia, hypocalcaemia and hypomagnesaemia are all conditions capable of eliciting a prolongation of QT. Prolonged QT in the context of hypokalaemia is associated with low voltage T waves and with U waves.

5.3 Ischaemic cardiopathy

During the evolution of a myocardial infarction giant negative T waves are associated with a long QT; their nature still needs to be clarified. This occurrence may be linked with an ischaemia-related action potential.

5.4 Other causes

Female gender [7, 8], hypothermia, total AV block, ventricular hypertrophy [13].

6. Arrhythmias associated with QT lengthening

Arrhythmias associated with QT lengthening include torsades de pointes (Figure 1) and ventricular fibrillation (Figure 2).

The above arrhythmias are elicited by oscillations of the membrane potential at times manifested during the 2nd and 3rd action potential stages. If the amplitude of these oscillations is sufficiently marked, extrasystolic beats potentially capable of triggering arrhythmias may occur. The onset of arrhythmia is correlated with a dispersion of repolarization facilitating the onset of the trigger factor.

A prolonged QT interval without any repolarization dispersion or the triggering of activities by membrane oscillations is not necessarily correlated with a significant risk of arrhythmic events. This is why some drugs, though they do prolong the QT interval, never, in the case of salbutamol, or rarely, as with amiodarone, induce arrhythmias [4, 5, 14].

In the course of an acquired long QT syndrome, ar-



Figure 1. Torsades de pointes

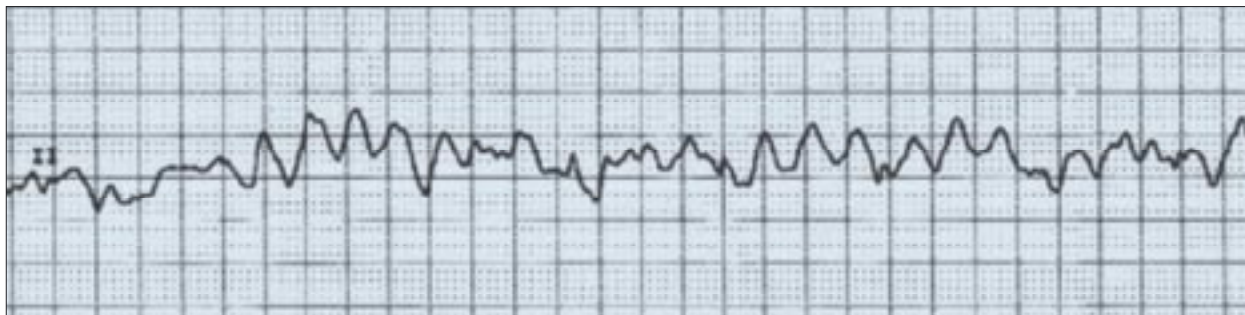


Figure 2. Ventricular fibrillation

rhythmias are often displayed without there being a low ventricular rate or any pauses. Conversely, arrhythmias correlated with a congenital long QT syndrome are induced through the involvement of the central nervous system.

In conclusion, recent studies providing evidence that a shortened QT interval may be correlated with arrhythmias and sudden death should be carefully noted. This electrophysiological alteration also correlates with genetic mutations that involve a malfunctioning of the potassium ion channel.

Three distinct forms of short QT syndrome linked with various gene mutations have been identified. Long QT is easy to define, because figures in excess of specific limit values are considered abnormal, but no clear-cut pathological limits have so far been defined for short QT.

A study performed to investigate short QT syndrome by applying the formula $QT_p = 656/(1+FC/100)$ in an attempt to establish a lower limit value for QT, provided evidence that, for a heart rate of 60 beats per minute, a QT below 361 msec should be considered pathological [9].

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Psychoactive Drugs and Prolongation of the QT Interval

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Summary

The links between psychiatry and cardiology that are pertinent to potential cardiovascular risks associated with the use of psychotropic drugs, especially antipsychotics, cannot be viewed as entirely new. In Italy, however, an important innovation was made when, on 28 February 2007, the Italian Medicines Agency (AIFA), issued a directive laying down provisions for the amendment of the printed papers that accompany various medicines, including haloperidol; that initiative has revived the relevance of the whole question. In particular, contraindications to the use of these drugs have been redefined. The primary ones are now listed as acute myocardial infarction, decompensated heart failure, arrhythmias treated with antiarrhythmic drugs belonging to special classes, the prolongation of the QT interval corrected for heart rate (QTc), the family history for arrhythmia or torsades de pointes, hypokalaemia and the concomitant use of drugs that prolong the QTc.

Key Words: Psychoactive drugs; QT Interval prolongation

In 1992 the Food and Drug Administration (FDA), the US Government Agency responsible for regulating and supervising the safety of foods and pharmaceutical products, made a request to the manufacturers of a terfenadine-based antihistamine to “warn” physicians that in some patients administration of that drug could lead to the onset of life-threatening cardiac arrhythmias. Five years later, in 1997, the FDA considered whether it should withdraw terfenadine from the market and, in the following year, 1998, two multinational drug companies, on their own initiative, decided to take all the products containing terfenadine off the market.

Similar events have happened with other drugs, including the effective prokinetic drug cisapride and the promising antipsychotic sertindole. These two compounds had likewise been implicated by the FDA in the potential onset of electrocardiographic alterations, especially prolongation of the QT interval, also known as “long QT”. A prolonged QT interval is sometimes associated with a specific form of ventricular arrhythmia, torsades de pointes (TdP) which, although it is often resolved spontaneously, may result in sudden cardiac death.

As to sertindole, the FDA presented evidence of an

association between the use of this antipsychotic drug and the lengthening of the QT interval, resulting in torsades de pointes and sudden cardiac death. In a clinical trial comprising over 2,000 patients, 27 deaths had been registered, of which 16 were caused by adverse cardiac events. A review carried out by an independent panel of experts later reported that no patients had experienced torsades de pointes, concluding that sertindole was not implicated in any of the 27 deaths. Furthermore, the authors of that review demonstrated that, at the time of enrolment in the trials, many of those patients had already been diagnosed with cardiac disorders, while pointing out the frequency of sudden cardiac death in schizophrenic patients. In spite of these findings, in 1998 the British Committee in Safety of Medicine, after it had previously authorized use of the drug, gathered new evidence on a potential association between sertindole administration and the onset of malignant arrhythmias, leading the drug manufacturers to take sertindole off the market.

In Italy, a directive issued by the Italian Medicines Agency (AIFA) on February 28th 2007, providing for the amendment of information sheets on various medicinal specialities, some of which had a history of long-stand-

ing, widespread use, such as chlorpromazine, haloperidol and sulpiride, once again brought to the fore the problem of the lengthening of the QT interval and its clinical importance.

1. Long QT and torsades de pointes

The QT interval, measured from the start of the QRS complex to the end of the T wave, is the time required for ventricular depolarization followed by repolarization. These two phases take up shorter intervals as heart rate rises, and a precise measurement can only be obtained after correcting the QT interval to take account of the heart rate (corrected QT or "QTc").

Over the last decade numerous definitions of long QTc have been published; pathological peak values of 450 msec both for adult males and adult females were unanimously agreed on only recently. Values of over 500 msec are considered a marker of increased risk of torsades de pointes and sudden cardiac death.

Torsades de pointes is a differentiated, polymorphic form of ventricular tachycardia named in recognition of the distinctive pattern taken by the ECG recording when peaks in the QRS complex seem to revolve around the isoelectric line; the high frequency of ventricular activation associated with this form of arrhythmia induces a marked decrease in cardiac load and arterial pressure. This arrhythmia may degenerate into ventricular fibrillation leading to sudden cardiac death. When there are specific predisposing factors, women appear to run a higher risk than men of developing TdP [3].

An especially high risk of torsades de pointes is run by patients featuring an ECG finding of a prolonged QT interval correlated to a congenital long QT syndrome (including the Romano Ward Syndrome and Jeville-Lange-Nielson Syndrome), electrolyte imbalance (hypopotassiemia, hypocalcaemia, hypomagnesiemia), as well as the administration of drugs such as phenothiazine, tricyclic antidepressants, macrolid antibiotics and several antihistamines (terfenadine, astemizole). Any failure to diagnose and adequately treat torsades de pointes may result in the onset of asphygmic ventricular tachycardia or ventricular fibrillation [24].

From a clinical standpoint torsades de pointes is invariably expressed through specific signs and symptoms, including vertigo, palpitations, fainting and syncope, leading to sudden cardiac death. Patients undergoing treatment with drugs potentially capable of inducing arrhythmias should therefore be carefully monitored for the onset of any signs or symptoms, to be duly correlated with the duration of arrhythmia (an episode lasting only a few seconds may only cause a slight vertigo, whereas a persistent episode may result in death).

The treatment of torsades de pointes implies withdrawal of the drug associated with the onset of symptoms, correction of electrolyte imbalance and acid-base equilibrium, the introduction of intravenous magnesium therapy

and temporary implant of a high frequency pacemaker to shorten the QT interval.

Fortunately, drug-induced torsades de pointes is not a common event, even if it is potentially life-threatening, and is closely correlated with duration of the QT interval (the longer the QT interval, the higher the probability of onset of torsades de pointes). The unforeseeable and probably idiosyncratic onset of this proarrhythmia suggests an underlying interindividual genetic variability of heart cell response to various drugs [20].

The action potential is given by the influx of sodium and calcium ionic currents, repolarizing potassium currents. Alterations to or a blockade of these currents induce a lengthening of the action potential, subsequently recorded on the ECG as a prolongation of the QT interval.

After performing a risk assessment, the influence of other predisposing factors should be taken into account (naturally, in addition to a family history of sudden death or syncope during childhood or early adulthood, particularly if correlated with physical exertion or emotional factors): old age, female gender, systolic dysfunction of the left ventricle, ischaemic heart disease, bradycardia, alteration of electrolyte balance (particularly hypokalaemia and hypomagnesiemia), alteration of renal and hepatic functions, and so on.

Moreover, pharmacodynamic interactions, such as those coming into play with the concomitant administration of multiple drugs potentially capable of prolonging the QT interval (e.g. class I and class III antiarrhythmic drugs), and pharmacokinetic interactions triggered by the concomitant administration of inhibitors and/or inducers of drug metabolizing isoenzymes belonging to the CYP450 complex (e.g. ketoconazole, grapefruit juice and cigarette smoking) should be carefully evaluated [1].

When prescribing a drug potentially capable of prolonging the QT interval, both the therapeutic role of the drug (effective need for the drug, and availability of equally effective alternative pharmacological treatments featuring a better safety profile), and patients' conditions should be carefully considered. It should, in any case, be stressed that in a population with a negative history and without any predisposing risk factors, an indiscriminate use of ECG prior to initiating treatment with a drug potentially capable of prolonging the QT interval is unjustified, in view of the fact that failure to detect ECG abnormalities does not rule out the presence of a masked predisposition. Lastly, it should be borne in mind that in patients undergoing treatment with drugs potentially capable of prolonging the QT interval, ECG measurement of the latter (or rather measurement of QTc) should be performed at peak plasma concentrations of the drug, taking into due consideration the concomitant administration (when present) of other drugs that interfere with the QT interval.

A list of drugs potentially capable of prolonging the QT interval is available on the website of the Center for Research on Therapeutics University of Arizona (<http://>

Table 1. Drugs and Torsades de Pointes (TdP)

Drugs associated with risk of TdP	Drugs potentially associated with risk of TdP	Drugs that should be avoided in patients with LQTS (long QT syndrome)
Drugs that regulatory authorities generally consider capable of increasing the risk of TdP	Drugs which, according to some reports, are associated with TdP but for which there is no clear evidence of correlation with an increased risk of TdP	Drugs to be avoided in patients diagnosed with suspected or has been diagnosed with congenital LQTS
Haloperidol Amiodarone * Quinidine * Cisapride Chloroquine Chlorpromazine Clarithromycin Disopyramide * Domperidone Droperidol Erythromycin * Methadone * Pentamidine * Pimozide* Procainamide Sotalol * Terfenadine Thioridazine	Alfuzosin Amantadine Atazanavir Azithromycin Chloral hydrate Clozapine Felbamate Indapamide Levofloxacin Lithium Moxifloxacin Nicardipine Ofloxacin Ondansetron Paliperidone Quetiapine Risperidone Salmeterol Tamoxifen Venlafaxine Voriconazole Ziprasidone	Amitriptyline Quinidine * Ciprofloxacin Citalopram Clomipramine Cocaine Desipramine Dopamine Doxepin Fluconazole Fluoxetine Galantamine Imipramine Itraconazole Ketoconazole Nortriptyline Paroxetine Sertraline Sibutramine Terbutaline Trimethoprim Trimipramine

* Adverse reaction occurred more in women than in men.

The table, as amended, is an extract of the tables published on the website of the Center for Research on Therapeutics, University of Arizona ([http // www.torsades.org / medical_pros / drug-lists.htm #](http://www.torsades.org/medical_pros/drug-lists.htm)) to which we refer for more details

www.torsades.org); this list is regularly updated on the basis of recent indications. Table 1 illustrates a limited example of drugs classified in three distinct categories:

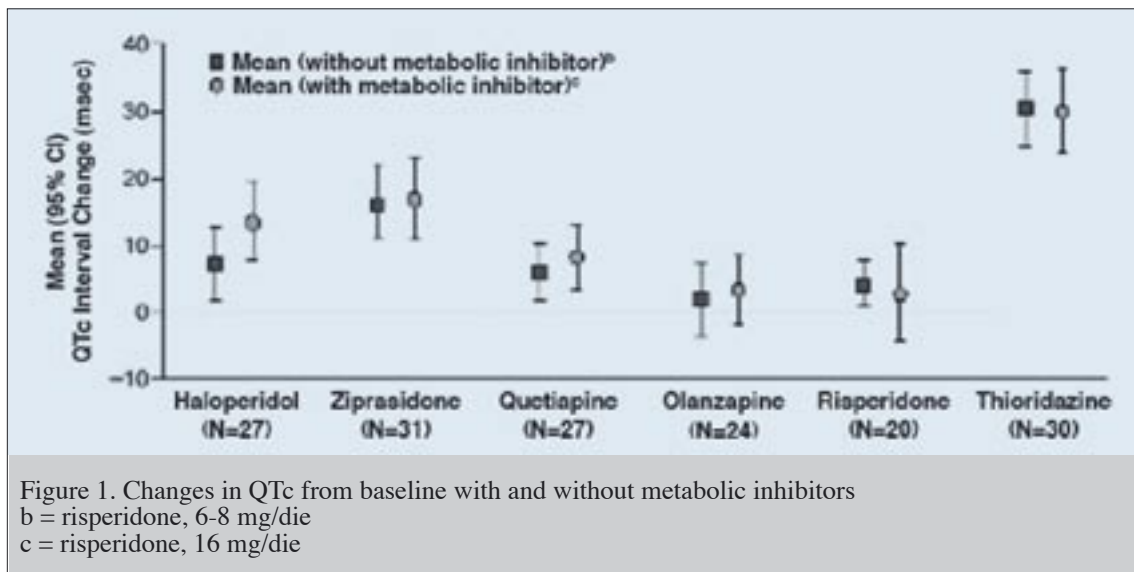
- 1) drugs correlated with a risk of TdP;
- 2) those potentially correlated with a risk of TdP;
- 3) those to be avoided in patients affected by the Long QT Syndrome (LQTS).

The first group, which includes methadone, accounts for psychiatric drugs such as haloperidol, chlorpromazine, droperidol, pimozide and thioridazine; the second group comprises clozapine, lithium, paliperidone, quetiapine, risperidone, venlafaxine and ziprasidone; the third group contains amitriptyline, citalopram, clomipramine, desipramine, doxepine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, trimipramine.

2. Antipsychotic drugs and prolongation of the QT interval

Evidence of the possible arrhythmic effect of antipsychotic drugs first became available in the 1960s, when several reports demonstrated a risk of TdP and sudden cardiac death correlated with treatment centring on thioridazine and mesoridazine [14]. The onset of alterations to cardiac rhythm during pharmacological treatment was initially viewed as an adverse event only affecting subjects who already had a cardiovascular disorder, but a large number of studies then demonstrated that drug-induced alterations of exactly that type also occurred in subjects not affected by cardiological conditions [17].

A study carried out over a three-year period (1985–1988) in Finland on 24,158 corpses analyzed by means of autopsy and toxicological tests, revealed that in approximately 49 subjects the cause of death could be “sudden death subsequent to administration of psychotropic drugs”, while adding that 46 of these individuals had been taking therapeutic doses of a phenothiazine, namely thioridazine [16].



In the literature numerous studies have provided evidence of an association of other antipsychotic compounds carrying a risk of inducing prolonged QTc [2, 6, 8]; on the other hand, unlike the findings reported for thioridazine, none of these drugs turn out to have been implicated in the onset of TdP. Likewise, although many case reports have been published in the literature on the onset of TdP after treatment with haloperidol, most of these cases involved subjects taking extremely high intravenous doses of the drug (up to 825 mg/24h) [11].

An open label study [10] performed to assess the effect of six different antipsychotics (thioridazine, haloperidol, olanzapine, risperidone, quetiapine and ziprasidone) on the QT interval revealed that thioridazine (30.1 msec) and ziprasidone (15.9 msec) showed the highest increase, while the lowest was recorded in subjects undergoing treatment with olanzapine (1.7 msec). Similar alterations were observed in patients undergoing concomitant treatment with P450 cytochrome inhibitors for each of the groups tested (Figure 1).

Behind thioridazine and ziprasidone, a group undergoing treatment with haloperidol displayed the highest degree of prolongation of the QTc interval (7.1 msec). The latter finding, in line with other studies [23], appears to reflect the IC₅₀ of the various compounds, an important biochemical parameter indicating the minimum concentration of the specific substance required to determine a 50% inhibition of a channel, an ionic current or any other type of biological parameter. A comparison between different drugs (Table 2) makes it clear that haloperidol features a markedly lower IC₅₀ than other antipsychotics; this gives the most plausible explanation for the increased propensity of the drug to inhibit hERG potassium channels and a correspondingly more marked lengthening of the QTc interval.

3. Antipsychotic drugs and cardiac risk

A recently published retrospective cohort study [19] carried out by a group of pharmacologists in Nashville, USA, to investigate a patient population aged between 30 and 74, has been given major coverage by the mass media in spreading the information that the use of second generation antipsychotic drugs, known as 'atypical antipsychotics', doubles the risk run by patients of sudden cardiac death. A risk of sudden death has long been reported too for first generation antipsychotics, known as 'typical antipsychotics'.

However, in the study under discussion the figures for the incidence of sudden cardiac death in patients undergoing treatment with typical and atypical antipsychotics were remarkably similar: approximately 1 out of 340 person-years in patients undergoing treatment with typical antipsychotics and 1 out of 360 person-years in those treated with atypical antipsychotics, compared to an incidence of 1 out of 700 person-years in individuals with similar characteristics not undergoing treatment with antipsychotics. The risk increased in a dose- and age-dependent manner.

Table 2. IC₅₀ of some antipsychotics

Drugs	IC ₅₀
Haloperidol	1nM
Risperidone	167 nM
Quetiapine	5765 nM
Olanzapine	6013 nM

Therefore, the study under review here argues that second generation antipsychotic drugs are no safer than their first generation counterparts, at least with respect to severe adverse cardiac events. The authors hypothesize that a higher incidence of sudden cardiac death is secondary to the onset of fatal arrhythmias, and is probably caused by the inhibitory action of the drugs on potassium channels, resulting in a prolongation of the cardiac repolarization rate.

Compared to antipsychotics of the first generation, those of the second generation are less likely to elicit extrapyramidal symptoms, tardive dyskinesias, and malignant neuroleptic syndromes, although they are more likely to induce weight gain and other metabolic disorders. Aripiprazole [9] features a lower likelihood of inducing a lengthening of the QT interval, one of the possible mechanisms underlying the modest increase in overall risk of sudden death in patients treated with antipsychotic drugs.

It should, however, be emphasized that in a patient with symptoms clearly indicating a need for treatment with antipsychotic drugs, the potential consequences produced by failure to administer these drugs may well exceed the risks involved in their use.

4. Regulations governing the use of psychoactive drugs carrying the potential risk of prolonging the QTc interval

On January 3rd 2005 the Italian Medicines Agency (AIFA), in agreement with regulatory bodies worldwide, issued a directive providing for the withdrawal from the market of thioridazine by the deadline of June 30th 2005 after “cases of prolongation of the QT interval, cardiac arrhythmias and sudden death” that had been reported in schizophrenic subjects undergoing treatment with the drug.

Two years later, the Official Gazette of the Italian Republic, no. 60, dated March 30th 2007, published a directive issued by the Italian Medicines Agency (AIFA) dated 28th February 2007 on the subjects of amendments made by manufacturers to product information sheets for several antipsychotic drugs. In the case of haloperidol, pimozide and droperidol, the modifications introduced focused on a series of contraindications to the use of the drugs under certain circumstances, including the presence of clinically significant cardiovascular disorders (recent myocardial infarction, heart failure, cardiac arrhythmias) and baseline conditions bringing a risk of cardiovascular events (lengthening of the QTc interval, family history of arrhythmia or TdP, low potassium levels). Furthermore, the concomitant use of other drugs capable of prolonging the QTc interval is prohibited, while recommendations were made to avoid prescribing concurrent treatment with other neuroleptics.

On product information sheets for drugs including amisulpiride, chlorpromazine, clotiapine, clozapine,

droperidol, levomepromazine, levosulpiride, perfenazine, promazine, quetiapine and risperidone, the warnings and precautions for use, interactions and adverse events were changed to include mention of the cardiovascular safety profile and problem of prolonging the QTc interval. Special emphasis was placed on the use of extreme caution in prescribing these drugs to patients affected by a past or present history of cardiovascular disorders or with a family history of prolongation of the QTc interval, advising against their concomitant use with other neuroleptics or electrolyte-altering drugs, and recommending a careful evaluation of the potential interactions of these drugs with other metabolic inhibitors. This directive enforced the document published by the Pharmacovigilance Working Party (technical committee of the European Medicines Agency, EMEA) entitled “Public Assessment Report on Neuroleptics and Cardiac Safety, in particular QT prolongation, cardiac arrhythmias, ventricular tachycardia and torsades de pointes” in May 2006, classifying the many antipsychotic drugs currently employed into three distinct categories on the basis of evidence reported in the literature with regard to the risk of prolonging QTc and inducing TdP (Table 3).

The list of antipsychotic drugs proposed by the Pharmacovigilance Working Party Group includes the drug olanzapine, not indicated afterwards in the AIFA directives for 2007 merely because the drug was already registered with EMEA; the criterion applied was that, even when modifications to product information details filed with EMEA were required, no further evaluations by regulatory bodies of other member states were needed, unlike the situation with other psychotic compounds that are only registered with national agencies.

The precautions for use and warnings provided for olanzapine, with specific regard to prolonging the QTc interval, should therefore be considered substantially similar to those reported for the group of antipsychotic drugs including quetiapine and risperidone. In a way contrary to the indications provided for the group comprising haloperidol, for the former group no contraindication is named with reference to the concurrent use of drugs capable of prolonging QTcs, but the warnings reported do advise against the concomitant use of other neuroleptics and/or other compounds displaying a similar risk of prolonging QTc intervals. In this connection, the directives’ marked impact on clinical practice, especially in a psychiatric context, has been clearly evident, focusing not only on the association between antipsychotics, but also on multiple drug treatment, including compounds belonging to other drug classes. It should be mentioned that on 14th February 2008 an AIFA Directive issued on 28th January 2008 was published in the Official Gazette of the Italian Republic, no. 38, referring to a risk of QT prolongation associated with lithium, one of the drugs most widely used in combination with antipsychotic drugs in patients undergoing a multiple drug treatment.

Table 3. Cardiac risk of some antipsychotics

Low	Medium	High
Loxapine Oxyperlina Perphenazine Pipotiazina Prochlorperazine Promazine Remoxipride	Amisulpride Benperidolo Chlorpromazine Clozapine Fluphenazine Flupentixolo Levomepromazine Olanzapine Quetiapine Risperidone Sulpiride Trifluoperazine Zotepina Zuclopendixol	Haloperidol Pimozide Sertindole Ziprasidone

5. Lithium

Lithium has unique features; it stands out as the sole example of a single ion capable of eliciting a potent mood-stabilizing action by means of a pharmacological mechanism that still needs to be fully understood. The therapeutic effect of the drug is correlated with the serum concentration of the ion, the optimal value to be achieved in the treatment of bipolar disorders being approximately 0.8 mEq/L. As a general rule, lithium levels are assayed 12 hours after the last oral dose, and most of the adverse effects are triggered when serum levels exceed 1.5-2 mEq/L.

A majority of Authors concur that the adverse effects produced by lithium on the cardiovascular system are relatively rare and of secondary importance [18]. Unlike the vast majority of psychoactive drugs, lithium is generally devoid of significant effects on the QTc interval; it may, however, elicit an inhibitory effect on impulse generation and transmission to the atrium. Accordingly, the latter may determine a risk of rhythm and conduction disorders, thus possibly explaining the small number of reports mentioning the onset of arrhythmias, together with several cases of bradyarrhythmia. ECG may exhibit a flattening or inversion of the T wave, and cases of atrioventricular block have been reported. Moreover, hypercalcaemia displayed in the aftermath of lithium's effect on parathyroid glands may predispose subjects to conduction defects, in particular bradycardia.

Lithium has, however, been included in the list compiled by the Center for Research on Therapeutics, University of Arizona, as one of the drugs potentially associated with the onset of TdP. For this reason, besides ensuring compliance with the AIFA Directive dated 28th January 2008, an ECG should be performed prior to initiating treatment with the drug.

6. Carbamazepine and other mood stabilizers

Carbamazepine is a versatile drug featuring a wide array of therapeutic indications: an antiepileptic and mood stabilizer, it is also prescribed for the treatment of trigeminal neuralgia. The drug interferes with sodium channels and, in addition to acting as a potent enzyme inducer in the liver; it exerts a chinidine-like effect on cardiac conduction. Structurally similar to tricyclic antidepressants, the drug may delay intracardiac conduction and the suppression of ventricular activity.

A study carried out by Kenneback in 1991 [15] demonstrated that carbamazepine produced no significant effect at ECG on the QRS or the QT interval in patients with a normal heart rate. However, patients with a pre-existing heart disease or arrhythmias displayed symptomatic conduction defects. ECG monitoring should therefore be scheduled, even though carbamazepine is not included on the list of drugs that set up a predisposition to prolonging the QT interval.

Various other substances displaying putative mood stabilizing properties are currently available. These include valproate and topiramate, neither of which has come under suspicion of inducing adverse cardiac effects. During use of lamotrigine isolated cases of atrioventricular block or supraventricular extrasystoles have been reported. Rare reports of bradycardia or atrial fibrillation have been signalled in the course of treatment with gabapentin. In any case, none of the substances just mentioned have been included on the list of drugs that favour a prolongation of the QT interval.

7. Tricyclic antidepressants (TCA)

Tricyclic antidepressants (imipramine, desipramine,

amitriptyline, nortriptyline, clomipramine, trimipramine, doxepine, protriptyline, amoxapine) have played a key role in the history of the treatment of depressive disorders. They were the first class of antidepressant compounds to be widely employed in the treatment of depression, constituting the treatment of choice for approximately 25 years.

The adverse effects produced by these compounds implied the need for psychiatrists to become familiar with a broad variety of symptomatological pictures, including the Central Anticholinergic Syndrome (CAS) comprising delirium and hallucinations; other side-effects include orthostatic hypotension, worsening of acute glaucoma and cardiac conduction delay.

Of the four pharmacodynamic mechanisms underlying the major adverse effects induced by TCAs – anticholinergic effect, adrenergic action, 5-HT₂ activation and antihistamine activity – only the first two, together with chinidine-like activity, are capable of affecting the cardiovascular system [5].

Cardiac arrhythmia is the main cause of death from overdose. For many years this primary consideration, together with the possible incidence of other conditions (orthostatic hypotension, one of the most common reasons for suspending treatment with tricyclic antidepressants; tachycardia, associated with all tricyclic drugs, not only those with a preponderant anticholinergic activity leading – especially in elderly patients and if continuing for long periods – to an increase in cardiac burden, of potentially high clinical significance in patients with ischaemic heart disease), made physicians exceedingly wary of prescribing TCA to patients either with or without cardiac disorders. The effects produced by these substances have been described in detail: by inhibiting the Na⁺/K⁺ATPase pump, tricyclic antidepressants apparently stabilize the excitable membranes, producing a dose-dependent conduction delay, particularly of ventricular conduction through the His-Purkinje bundle. Thus, tricyclic antidepressants possess type Ia antiarrhythmic properties or chinidine-like effects [7].

In patients featuring a pre-existent cardiac conduction delay, therapeutic plasma concentrations of tricyclic antidepressants may produce positive effects on ventricular excitation; however, TCAs are also capable of eliciting a further delay in the conduction rate, leading to cardiac arrest. Prior to treatment, a QTc interval > 450 msec is indicative of the presence of an overt conduction delay; in these cases TCA should not be administered on account of the danger of worsening patients' conditions. High plasma concentrations of the drug imply an increased risk of cardiotoxicity; for example, concentrations of imipramine exceeding 350 ng/ml are known to increase a high-grade atrioventricular block.

Children below the age of 12 years display a greater susceptibility to the risk of sudden death during treatment with tricyclic antidepressants; cases of sudden

death have been reported in a limited number of children aged below 12 affected by attention/hyperactivity deficit (ADHD) who had been taking desipramine. It has been hypothesized that an immature conduction system may render some children more vulnerable to the cardiac effects of desipramine.

In view of the above problems of cardiac tolerability, associated with the recent finding of a good safety profile for sertraline (SSRI) [22] in treating depressed patients after myocardial infarction, the use of TCA is largely contraindicated in patients affected by ischaemic heart disease, and these drugs should be administered only to patients who fail to respond positively to other drugs.

8. Other antidepressants

The antidepressant venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has shown greater efficacy in inhibiting the reuptake of serotonin (5-HT) than noradrenaline (NA); in vitro studies have indicated a higher, almost 8-fold affinity of venlafaxine for the 5-HT than for the NA transporter. It appears, therefore, that at low doses (75–150 mg/die) venlafaxine acts prevalently on serotonin, later inhibiting reuptake by both neurotransmitters in a dose-dependent fashion.

A wide variety of symptoms comprising ECG abnormalities (lengthening of the QT interval, branch block, prolongation of QRS), sinus and ventricular tachycardia, bradycardia, hypertension, alteration of consciousness (from lethargy to coma), serotonergic syndrome and comitial crisis have been reported in cases of acute but non-fatal venlafaxine overdose.

At doses exceeding 200 mg/die, venlafaxine is capable of inducing prolongation of the QT interval in young healthy adults [12]. Data reported by coroners in England and Wales between 1998 and 2000 have implicated venlafaxine in 12.7 deaths per million prescriptions, which was substantially higher than for SSRIs and at a level similar to that for tricyclic antidepressants (1.9 and 12.6 deaths per million prescriptions, respectively) [4].

Duloxetine is another serotonin-noradrenaline reuptake inhibitor (SNRI). Compared to venlafaxine, duloxetine appears to achieve a better balance between the two pathways, producing a more marked influence on NA than 5-HT reuptake.

Clinical trials have demonstrated the good degree of safety and tolerability of duloxetine when administered at a dose ranging between 40 and 120 mg/die. A slight but significant increase in heart rate (tachycardia) has been reported even at low doses of the drug [21].

Duloxetine does not appear to produce any significant adverse effects on cardiac repolarization or the QT interval. A clinical trial performed [25] using duloxetine doses higher than those prescribed for therapeutic purposes (400 mg/die) demonstrated a decrease in QTc, not exceeding 36 msec with respect to baseline values, with no subjects displaying a QTc > 445 msec.

Citalopram may determine a non-specific, clinically insignificant prolongation of the QT interval; escitalopram appears to elicit effects similar to those obtained with citalopram. After citalopram overdoses, a prolongation of the QT interval has been observed [13].

9. Conclusions

To conclude, psychiatric patients undergoing pharmacological treatment – with particular reference to subjects affected by psychotic disorders – are notably susceptible to severe cardiac disorders, including rhythm abnormalities, ischaemic heart disease and myocarditis, but also to a wide array of associated risk factors. To be specific, these comprise type II diabetes mellitus, metabolic disorders, obesity, cigarette smoking and substance use, as well as other hazardous practices. Further studies should now be undertaken to assess the problem of prolongation of the QT interval in various clinical contexts.

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Opioid Treatment and “Long-QT Syndrome (LQTS)” : a Critical Review of the Literature

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Summary

The present paper aims to provide a critical survey of the current literature on QT-related cardiac safety in cases of methadone treatment. On the whole, case reports, whether single or multiple, do not seem to offer a reliable basis for drawing conclusions about the weight of any putative risk factor in QT prolongation. Systematic studies, on the other hand, do allow certain statements to be made about the extent and the importance of QT prolongation during methadone maintenance treatment for heroin addiction. There do not seem to be any major concerns about cardiac safety arising from methadone itself in the average addict. Higher risk conditions due to multiple and polydrug treatments deserve more intensive surveillance. From a risk/benefit perspective, there is no clear rationale for applying a dose ceiling.

Key Words: Opioid Treatment; Long-QT Syndrome; Review

1. Long QT Syndrome (LQTS): definition and clinical parameters

A survey of the critical literature shows that the acronym QT is currently interpreted as QTc (i.e. QT corrected for heart rate) [6, 25, 63].

The long QT syndrome (LQTS) is characterized by a disposition towards lengthening of the QT interval for no known reason, implying an increased risk of ventricular arrhythmias including torsades de pointes and ventricular fibrillation (with the former sometimes evolving into the latter) [49, 52, 53, 68].

A diagnosis of LQTS is based on the finding of a long QT indicating the likelihood of a future onset of clinical manifestations associated with the syndrome. The values recorded went from 0.41 sec to 0.65 sec, a range making them comparable with those obtained from many subjects with a normal QT interval [26]. In particular, 10% of subjects display an initial QT value no higher than 0.44 sec, and 30% between 0.45 and 0.47 sec, with a mean of 0.49 sec. Threshold values for a casually observed ‘suspect’ prolongation of QT vary: some authors suggest 0.48 sec for women and 0.47 sec for men [69], whereas

others propose 0.46 and 0.45 sec, respectively [53]. A diagnosis of LQTS may at times be formulated in the 0.41-0.47 sec range for males and 0.43-0.48 sec for females; below this threshold an LQTS diagnosis becomes highly unlikely. The Italian Medicines Agency (AIFA) indicates values below 0.43 and 0.45 sec as normal in adult men and women, respectively; 0.45 and 0.47 sec constitute borderline values and 0.45 and 0.47 sec indicating the presence of LQTS [59, 61, 74].

Since a ‘tail’ of QT value distribution in arrhythmic patients overlaps QT, lengthening can be applied as a risk factor allowing discrimination. Prolongation exceeding 30 msec is at risk, whereas an increase going beyond 60 msec shows that a critical threshold has been passed [31, 63]. In the course of ventricular arrhythmias, or shortly before their onset, the QT interval tends to increase progressively, reaching values exceeding 0.5 sec [7]. As no clear-cut association can be established between long QT and LQTS for values below 0.5 sec, this value is considered the clinically specific threshold (whether observed in the course of arrhythmias or immediately prior to their onset). Therefore, values ‘at risk of prolongation’ are highly variable, though it can be stated that values

exceeding 500 msec will only be reached if baseline levels were initially close to this threshold.

In conclusion, an ECG finding of a prolonged QT interval bridges the gap, with a certain margin of error, between the genetic, or acquired 'patophysiological' basis of LQTS and its clinical expression. Thus, subjects with a QT interval exceeding 0.5 sec, and a recent lengthening of QT interval of 40 msec or more, corresponding to a final QT value of over 0.41 sec, should be considered at risk of arrhythmia [59]. An additional parameter to be considered is a QT dispersion of more than 100 msec [40]. In a 12-lead ECG recording, dispersion of the QT interval (QTd) is the difference between the longest and the shortest QT interval, and is used to assess the difference in ventricular repolarization.

LQTS features a broad array of genetic, molecular and patophysiological structures [66, 67]: when corresponding to an alteration of phase III K⁺ currents (with LQT1, LQT2, LQT5, LQT6 covering 90% of all cases), torsades de pointes (TdP), at times evolving into ventricular fibrillation, may be observed. The LQT3 form, linked to the gene coding for the voltage-gated Na⁺ channel (SCN5A), is mainly expressed as ventricular fibrillation without TdP (10% of cases) [8-10, 16, 35, 68].

Cases of LQTS in a pure form are extremely rare (only 1 in 5000), although studies are currently under way to ascertain the associated genes. A clear majority of cases feature combined risk factors, at least partly concurrent with the manifestation of arrhythmias (acquired or 'mixed' forms).

The physiopathology of acquired forms of LQTS is comparable to that observed in forms of genetic origin, the only substantial difference being that it is induced by external factors. As a result, the ECG parameters featured are similar. A predisposition to acquired LQTS is not determined merely by genetic factors, but rather by a series of congenital and acquired factors that still needs to be fully clarified. Accordingly, additional unknown factors may be implicated in eliciting a varying response to a drug capable of prolonging the QT interval. As to the drug-induced risk threshold for LQTS, in cases of torsades de pointes appearing after the initiation of treatment for non-cardiac issues, as many as 92% had QT values exceeding 0.5 sec [7]. The risk threshold may therefore be fixed at 0.5 sec.

In the group of LQTS associated with specific drugs, additional risk factors may be involved, including: female gender (70%) [18, 45], hypokalaemia (39%), pre-existing structural cardiac disorders (41%), multiple drug treatments with drugs capable of prolonging the QT interval (28%) [14, 62, 70]. An association between drug-induced LQTS and a genetic substrate for LQTS is found in 18% of cases, so demonstrating that there is no precise clinical separation between genetic and acquired forms. The genetic forms tend to be clinically manifested in the presence of acquired factors [51]. The mechanism through which drugs induce LQTS is linked

to an interference with the channel-proteins that regulate cardiac repolarization. In particular, methadone interferes with the subunit encoding for the HERG/LQTS2 gene. The latter interference is not linked to the opioid activity being expressed; in fact, several opiate drugs, such as methadone, phentanyl and LAAM produce a markedly higher degree of interference (two orders of magnitude) compared to morphine and codeine [34].

2. LQTS and methadone treatment: a review of the literature

The definition of drug-related risks implies a systematic monitoring of patients. For drugs already on the market, a risk assessment should be carried out, taking into account the frequency of adverse cardiac events or an 'excessive' cardiac mortality rate among users of the drug since its introduction. In this connection, a positive long-term general safety profile has been demonstrated for methadone [12, 29, 32, 54].

In the absence of consistent retrospective evidence, recent warnings may reveal the expression of a selective focus on a single putative risk factor, and thus be biased by previous warnings issued on the same subject (e.g. the most likely rationale underlying the publishing of case reports seems to be the previous publication of similar case reports). The emergence of a risk of LQTS in subjects in long-term treatment with a specific drug who have shown no signs of adverse cardiac events suggests that increasing attention should be focused on new potential risk factors affecting recent consumers of that drug. With regard to methadone-maintained subjects, these factors may be associated with an increased use of anti-retroviral or anti-infective drugs, due to favourable therapeutic conditions induced by methadone treatment, or with an increased use of psychiatric drugs due to the furthering of knowledge of the association between opioid dependence and mental illness [28, 60, 73].

Substance abuse, in particular of alcohol and cocaine, may constitute an additional erratic, but still significant, factor [41, 55].

2.1 Case reports and case series

The practice of case reporting may, indeed, provide useful indications for research. On the other hand, a methodological distinction needs to be made between primary and secondary case reports. Secondary case reports are those with a rationale based on previously published primary reports that may have stimulated a selective focus on a given aspect or factor. In other words, secondary case reports feature no degree of spontaneity or originality. When secondary case-reports continue to be submitted to journals in spite of the publication of studies performed on larger samples, they become virtually superfluous, because the scientific value of a large body of secondary reports is no higher – statistically speaking

– than that of the original ‘primary’ report.

Naturally, when many reports all focused on a single drug build up over a relatively short period, that seems to suggest that a greater risk is attached to the drug concerned, but only as long as the presence of other risk factors in the sample can be ruled out. The publication of a series of reports on any given drug (e.g. methadone) known to be associated with other risk factors may well be due to a particular show of interest in that specific drug, so providing only a partial view of the actual epidemiological weight of the drug. When dealing with a syndrome such as LQTS, whose clinical expression is probably based on a range of precipitating factors, an observation focusing on a single factor in a selected population may well prove to be biased.

On the whole, case reports published on methadone and LQTS [27, 39, 50, 64, 71] essentially indicate that a combination of a series of arrhythmogenic factors may lead to the onset of torsades de pointes in subjects who have no pre-existing (genetic) predisposition to LQTS. Findings like these should not be viewed merely as ‘examples’ of methadone-related arrhythmias, but rather as cases strengthening the view that methadone administration may lead to the onset of arrhythmias.

Prospective evidence basically points to a normalization of the QT interval after an arrhythmic episode, once the methadone dose has been reduced or discontinued. This finding is not, however, sufficiently specific, in view of the fact that, theoretically, the discontinuation or reduction of other concomitant treatments may also lead to QT normalization and a fall in the risk of arrhythmias. As an example, out of a total of 4 cases studied by Gil [27], the QT interval returned to normal (0.38 sec) in only one patient after methadone discontinuation, although the methadone-free mean recorded was 0.47 sec. In ten cases described by Piguet [58], QT was shortened following a reduction of both methadone and other concomitant drugs. Moreover, in the course of treatment of arrhythmias, potential risk factors (e.g. electrolyte imbalance) are obviously monitored. Sticherling described five cases, all of them comprising additional risk factors for prolongation of QT interval that, once corrected, led to the normalization of QT values [65].

Not all case reports refer to a therapeutic setting or to the administration of prescribed dosages. A report published by De Bels [13] provides details of two cases of overdose from non-therapeutic administration of street methadone within a context of polydrug abuse, while one of the cases described by Walker refers to a rapid dose-escalation from 330 to 880 mg/die over the days immediately prior to an arrhythmic episode due to insufficient pain coverage [71]. The patient described in a report by Decerf [15] died three days after the abrupt reintroduction of methadone at a previously administered dose of 130 mg/die subsequent to a twelve-day withdrawal period.

In a study investigating 17 individuals, Krantz [38] indicates methadone as the only common predictive factor,

in spite of the presence of other, more variable risk factors. Moreover, only subjects with a QT interval exceeding 0.5 sec were included in the study. The finding of a dose-QT correlation is therefore not a naturalistic observation, as it only includes subjects showing a pathological prolongation of QT interval and signs of LQTS.

A correlation between methadone dose and QT detected in patients who had been referred for treatment of arrhythmias or arrhythmic syncope is only significant when related to patients affected by arrhythmia, not to methadone-treated subjects in general.

In a review of 40 cases, Justo and co-workers stressed that all patients (affected by clinically diagnosed LQTS) featuring a pathological lengthening of the QT interval (mean 598 msec), were taking high doses of methadone and, in approximately 25% of these cases, were marked out by other single or combined risk factors for QT prolongation. In particular, about 1 patient in every 4 was suffering from a cardiac disease, with an even higher rate of liver or kidney failure. 40% of subjects were HIV+ and 35% presented hypokalaemia [33]. The limitations observed were similar to those revealed for single case reports or case-series.

2.2 Arrhythmic mortality and long QT in methadone-treated subjects

Data provided by the FDA (Food and Drug Administration) confirm that 0.78% (59 cases) of adverse events reported during methadone treatment from 1969 to 2002 took the form of TdP, with 3 out of 4 cases displaying additional risk factors for LQTS [56]. A retrospective study of 2382 patients reported an estimated death rate of 0.06 per 100 patient-years [2].

Fanoie et al. carried out a study to investigate the correlation between therapeutic status and a history of syncope in a group of 450 heroin addicts, demonstrating a correlation between doses exceeding 50 mg and probable onset of syncope. No clear-cut results were, however, obtained due to the difficulties encountered in defining syncopal episodes [22].

In a group monitored by Peles, 3 patients displaying a prolongation of the QT interval of over 500 msec had all died from other causes at two-year follow-up [57].

2.3 Long QT in methadone-treated subjects: prospective, cross-sectional and retrospective studies

Overall, most of the studies present in the literature report mean QT values below the 450 msec threshold [4, 11, 30, 46, 47].

In a prospective study undertaken by Wedam to compare equally potent doses of buprenorphine, methadone and LAAM, 21% of subjects displayed QT values exceeding 470 msec (males) or 490 msec (females) throughout a 17-month treatment with methadone, yielding a result intermediate between findings obtained with LAAM

(28%) and buprenorphine (0%). Approximately 11% of methadone- and LAAM-treated subjects displayed QT values of more than 0.5 sec in at least one monthly ECG recording performed throughout the study period (vs. 0% on buprenorphine). Methadone-related prolongation of the QT interval occurs gradually over the first 8 weeks, contrary to observations made with other drugs; this could be due to a diverse rapidity of dose-escalation, or to pharmacological differences between the compounds [72].

In a study published by Peles (in a predominantly male sample), approximately 16% of subjects presenting a prolonged QT exceeding 450 msec in the course of methadone treatment lasting from 3 months to several years. Contrary to previous studies, prolongation of the QT interval to over 0.5 sec was only observed in 3 (2%) of these subjects [57].

Cruciani and co-workers observed a mean value slightly below the threshold for risk (428 msec), even if 33% of subjects studied presented a prolongation of QT interval. In any case, no high-risk values (>0.5 sec) were detected [11].

Maremmani et al. reported QT values for subjects on methadone treatment somewhat higher than expected as to age and sex, although exceeding 0.5 sec in just 2 cases; none of these subjects had any previous history of cardiovascular events [46]. Similarly, Fonseca and colleagues found a moderate prevalence (9.2%) of high QT values (> 440), but rarely (1.8%) higher than 500 msec [23].

A cross-sectional controlled study performed on a small group of methadone-treated subjects found no difference between methadone and buprenorphine, reporting a tendency towards higher values within the safety range (405 msec) in subjects taking methadone doses of over 60 mg/die [4].

In a study undertaken by Ehret and co-workers, 16.2% of patients displayed a QT above 500 msec versus 0% in the control group; 3.6% (6) of subjects showed TdP, although the weight of methadone as a causal factor for the onset of TdP in this subgroup was calculated to be approximately 30%. It should be noted that all the patients studied were heroin addicts admitted to hospital for various reasons. The sample displaying TdP were all polydrug users (median 9 vs. 4 in the control group) [19].

2.4 *Prospective studies on QT prolongation in subjects on methadone treatment*

With specific reference to prolongation of the QT interval in the course of methadone treatment, Krantz [37] reported an average increase in QT of approx. 14 msec at 6 months; Wedam and co-workers [72] 17 msec in at least one recording performed during the stabilization period (subsequent to the first month); Martell reported a 12 msec prolongation at 6 months and 11 msec at 12 months [47]. Chronic pain patients switching from mor-

phine to methadone displayed a very limited (5 msec), but still significant increase in the QT interval [24]. Fanoë calculated an increase of 0.14 msec/mg oral methadone: considering a mean effective dose (80-120 mg/die), this would correspond to approximately 14 msec [22].

A prolongation of the QT interval beyond 60 msec was observed in 12% of cases (intermediate between the 21% reported for LAAM and 2% buprenorphine) in the study carried out by Wedam and colleagues [72].

A mean 7-8% increase should be expected over the first two months of treatment. The final value reached is invariably below the 450/470 msec threshold in substance-free subjects [30].

It would seem that the finding of a prolongation of the QT interval is a relatively frequent occurrence [30, 72]; when compared to values obtained in controls (detox, pre-treatment), any methadone-related lengthening is invariably quite limited [22, 24, 30, 47, 72]. In studies performed on samples of asymptomatic subjects, the finding of risk values is a relatively rare event, and is most frequently observed, as might be expected, in selected hospitalized samples.

Dispersion of the QT interval never exceeded 0.1 msec, although an increase was observed in subjects on concomitant treatment with methadone and antidepressants [37].

Athanasos and co-workers [4] specifically report a higher dose-dependent rate of U waves in ECG recordings from subjects on methadone rather than buprenorphine treatment. This finding confirms the frequent observation (32%) of U waves in methadone-maintained subjects [44]. The waves observed are 'physiological' U waves, merging with T waves and thus included in measurement of the QT interval [1].

The final interpretation of the findings obtained in several of the above studies has a rather limited scope, however. At variance with other studies, the paper that reported the highest percentage of cases in which QT lengthening went beyond 0.5 sec [72], while it provided no details of drug abuse, ruled out the involvement of prescription drug-related pharmacological factors; its inclusion criteria was simply that of a prolongation of the QT interval recorded in at least one monthly ECG: a prolongation of that kind could have been no more than a chance finding.

The results obtained by Fanoë [22], in a study comprising subjects with a history of syncope treated with low doses of methadone — subjects who had not necessarily been stabilized — cannot however be adequately interpreted to allow for a risk-benefit assessment. Maremmani and co-workers attempted to investigate a sample of stabilized heroin addicts free from all other substances of abuse, who then underwent methadone treatment at a mean dose of approx. 90 mg/die. In their sample, which was selected for its suitability for a risk-benefit assessment, a 2.4% incidence rate was reported for prolonged QT, with no relevant clinical associations [46].

Injectable methadone can likewise induce prolongation of the QT interval. The study carried out by Mayet and coll. [48] had the major limitation that it did not rule out the possible concurrent use of cocaine, which was documented in 53% of subjects on enrolment. Episodes of QT lengthening were observed quite frequently, although no constant values were obtained and prolongation could not be associated with any specific ‘acute’ action. Kornick and coll. found a dose-dependent average prolongation of 41 msec (measured before and after i.v. methadone) compared to 9 msec with i.v. morphine, which, incidentally, demonstrated the weaker effect on QT produced by the solvent chlorbutanol. The latter study was a retrospective observation of inpatients suffering from neoplastic diseases who had been taking methadone for pain control purposes [36].

2.5 Quantitative correlations

Generally speaking, no constant dose-effect correlation has been reported. It is, however, true that Peles et al. observed a more marked prolongation of the QT interval at methadone doses exceeded 120 mg, even if no dose-effect correlation could be confirmed [57].

A similar, small but significant correlation (2 msec mean difference) was revealed by Martell in subjects taking methadone doses over 110 mg/die [47]. Athanasos and co-workers reported a difference in QT prolongation with methadone doses below and above 60 mg/die, but invariably below risk values (381 msec vs 405 msec) [4]. Cruciani and colleagues found a correlation only in male subjects on methadone for less than one year [11], a finding not confirmed by Marenmani [46].

In the treatment of addiction, it is noteworthy that oral methadone doses correspond to blood methadone levels that may vary widely: by contrast, doses that exceed 200 mg correspond to a narrow range of blood levels, due to a faster hepatic metabolic rate [42]. When higher doses are administered to chronic pain patients, they may actually correspond to higher blood methadone levels, and rapid dose escalation can be resorted to in treating renewed pain. In the multiple case report published by Krantz, blood methadone levels were referred to as being “higher than expected”.

It can be concluded that the rationale underlying the administration of high doses of methadone in the treatment of drug abuse differs from that applied in the treatment of chronic pain. In the latter case the use of extremely high methadone doses probably leads directly to an effective increase in expected blood methadone levels.

Methadone is produced as a racemic mixture. The inactive isomeric S form displays a higher (3.5-fold) potency than the hERG current [43]. Special care should therefore be taken in managing the drugs which act as inhibitors of the S-methadone metabolism that is regulated by CYP2B6 (the substrate-inhibitors ifosfamide and cyclofosfamide, thiotepa, ticlopidin, efavirenz and

bupropion). Subjects displaying a slow metabolic clearance of S-methadone — those running a particularly high risk of LQTS — accounted for 6% of the sample studied by Eap and co-workers [17].

On the contrary, Fonseca and colleagues failed to detect any correlation between plasma concentration of isomers and QT values [23].

Turning now to the metabolic interactions with active R-methadone isomers, mainly CYP3A4 and 2D6 inhibitors, no additional methadone-related risks are actually expected when doses are titrated on a clinical basis, as blood methadone levels will be higher than expected, corresponding to lower oral doses.

An increased risk of LQTS may, however, be implicated when methadone administration is associated with drugs known to raise blood methadone levels and prolong the QT interval. The concomitant administration of drugs known to increase blood methadone levels may create a false impression of a drug-induced improvement of psychiatric symptoms, when this is actually produced by an increase in blood concentrations; in these cases, the QT interval may be prolonged to a greater extent than it is after the administration of a higher dose of methadone.

3. Buprenorphine and lengthening of the QT interval

Studies undertaken to investigate buprenorphine provide indications confirming the relative neutrality of the drug with regard to the risk of prolonging the QT interval. Two prospective studies failed to find any cases of long-term prolongation of the QT interval exceeding 450 msec (or 470 in females) [72]. Likewise, in a retrospective study of 200 cases, none of the QT values exceeded 450 msec [72].

Despite this, a few (2%) cases of pathological ‘lengthening’ beyond 60 msec may be observed, without ever reaching the threshold for risk values. [72]. As a general rule, subjects treated with buprenorphine alone are not susceptible to significant changes in QT values [5].

In a comparative cross-sectional study, buprenorphine was seen to be associated with QT values similar to those found during methadone treatment and in control groups [4], while a further study performed to compare methadone with LAAM showed that buprenorphine - neutral - gave results that differed from those of the other two treatments [72].

Two incidental findings have been described in which buprenorphine was administered as an alternative to methadone in subjects developing overt clinical LQTS [21, 37].

4. Recommendations

The evidence provided suggests the advisability of great caution in managing methadone-treated patients featuring multiple risk factors for ventricular arrhythmias.

As a general rule, in the course of methadone treatment a prolongation of the QT interval not exceeding threshold risk values can be expected. The extent and frequency of QT lengthening are considerably lower than those reported for LAAM [72], which was withdrawn from the European market because it raised the risk of arrhythmias [20]. The following recommendations may therefore be put forward for the task of defining and monitoring arrhythmias in methadone-treated patients:

a) patient and family history of LQTS (recurrent syncope of unknown origin, sudden death) should both be ascertained;

b) potential drug-associated risk factors for LQTS should be recorded;

c) ECGs whose aim is to identify cases of overt LQTS should only be resorted to before the start of treatment if and only if a given case includes known and/or suspected risk factors. If subjects of this kind are treated with methadone, an ECG should then be performed periodically to monitor developments, as an onset of LQTS could occur during treatment. The above procedure should also apply when there is a positive history, or with the use of cocaine or any other illicit substance capable of prolonging the QT interval;

d) avoid the association of methadone with drugs capable of prolonging the QT interval [3], unless strictly necessary, particularly in the case of double diagnosis and when prescribing drugs that inhibit the methadone metabolism. When a drug association is required, an ECG should be performed to monitor for variations in QT length;

e) on the basis of the risk parameters displayed (length, prolongation, dispersion) and also of the range of risks involved, the possibility of resorting to alternative treatments or lower doses should be taken into account in stabilized patients undergoing long-term treatment, or other concomitant treatments modified according to an established scientific hierarchy, bearing in mind that a discontinuation of methadone treatment may also affect compliance with other associated treatments (e.g. anti-infective or psychiatric drugs);

f) in LQTS cases that comprise critical episodes, establish an alternative treatment or assess the suitability of a pacemaker implant.

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Management of Cardiac Risk during Methadone Treatment: Focus on the QT Interval

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Summary

In recent years, methadone, along with various other drugs, has been implicated in the lengthening of the QT interval of the electrocardiogram (ECG) and in the onset of potentially fatal arrhythmias. The risk of prolonged QT in methadone-maintained subjects is estimated at between 2-4%, while the risks of torsades de pointes or sudden death are extremely low. Despite the diversities reported, the guidelines available to date indicate the need to implement preventive measures based on ECG screening. The impact of these recommendations is, however, limited by the lack of a comparative risk/benefit assessment of specific procedures.

Key Words: QT Interval; QTc; ECG screening; Torsade de Pointes; Cardiac Risk; Methadone Treatment

1. Introduction

Methadone maintenance treatment is still recognized as the gold standard in the effective pharmacological treatment of opioid dependence [5, 11, 23, 24]

In recent years many reports have been published in the literature on cardiac side-effects elicited by the drug on electrical conduction in heart tissue. Indeed, along with various other drugs, methadone has been implicated in the lengthening of the QT interval observed in electrocardiogram (ECG) and in the onset of potentially fatal arrhythmias. Methadone shares this feature with LAAM, whereas buprenorphine does not appear to produce any significant effect on QT [16, 30].

Prolongation of the QT interval is an outcome of an alteration of electric activity in the left ventricle that is capable of eliciting disorders in its rhythm, including torsades de pointes and ventricular fibrillation. The blockade of hERG K⁺ (human ether-a-go-go-related gene) channels in the heart, which is involved in the formation of IKr (rapid delayed rectifier) currents probably underlies QT prolongation [7].

Lengthening of the QT interval may be caused by genetic and acquired factors, such as pathological conditions

or medications, methadone included, that are capable of affecting electrical conduction (hERG channels).

This problem is therefore directly pertinent to most of the subjects who undergo methadone treatment for opioid dependence (approximately one million people worldwide) or pain management.

Reports published in the literature on this topic point to the onset of torsades de pointes in patients treated with high doses of methadone (range 65-1,000 mg), often associated with additional risk factors (hypokalaemia, administration of other hepatic microsomal system inhibitors) [17, 26, 27]. Other findings obtained in prospective studies performed to investigate patients treated with doses ranging between 30 and 180 mg reported a prolongation of the QT interval but a lack of torsades de pointes [17, 21, 22]. Several of the studies surveyed in this connection reported a correlation between prolonged QT interval and drug dosage.

Moreover, cross-sectional studies carried out on patients treated with doses of methadone ranging from 10 to 1,200 mg daily revealed a prolongation of the QT interval in 30-80% of subjects [6, 10, 12, 20, 28]; several of these latter studies also reported a correlation with methadone doses.

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The main risk factors for prolonged QT interval and the possible onset of arrhythmias in patients undergoing methadone treatment are associated with genetic factors, physiological and pathological conditions, and with a wide variety of drugs.

2. Genetic factors

Approximately 2% of the population carries a polymorphism of the hERG channel gene that underlies the presence of a congenital long QT syndrome. The clinical form taken by the latter syndrome may be manifested through arrhythmic episodes during physical exertion, emotional stress or sleep, although many subjects remain asymptomatic. However, these genetic structures increase the susceptibility of bearers to the effects of hERG channel blockade by methadone [1].

It should also be taken into account that the methadone metabolism, which is closely linked with the hepatic microsomal P450 system, is genetically regulated. Involvement of the cytochrome polymorphism CYP2D6, which is responsible for alteration of the metabolic rate in one of the two enantiomers of methadone (S), is particularly well-known. Indeed, ultrarapid, rapid and slow metabolizers of methadone have been identified on the basis of the genetic characteristics of the population for this isoenzyme. Slow metabolizers are subject to increased plasma concentrations of methadone leading to an increased risk of prolonging the QT interval [10].

3. Pharmacokinetic factors

Methadone is largely metabolized through the activity of enzymes present in the cytochrome P450 system. Reports in the literature specify the CYP1A2, CYP2D6, CYP3A4, CYP2C9, and CYP2C19 isoenzymes, although the exact contribution provided by each isoenzyme still needs to be ascertained.

Previous studies have demonstrated the existence of an individual inter- and intra-variability in the enzymatic activity of these cytochromes, producing a differential effect on the two methadone isomers: the R isomer underlying the anticraving and analgesic effects of the drug, and the S isomer, which exerts only a bland anticraving activity, but is capable of blocking hERG channels 3.5 times as effectively as methadone R [10]. In view of the variability in the enzymatic activity of the isoenzymes implicated in the methadone metabolism, particularly CYP2D6, patients taking identical doses of methadone may display as much as a 58-fold variability in plasma concentrations. When limiting evaluations to patients taking no other medications besides methadone, inter-individual variability decreases to 35-fold for methadone on the whole and 17-fold for R-methadone [9]. This variability may at least partly explain the discrepancies reported with regard to the correlation between methadone dose and prolongation of the QT interval.

Various other drugs may interfere with methadone by acting on the different stages of absorption, protein binding, metabolism, and excretion. Studies investigating a potential interference at the level of the microsomal P450 system have recently been undertaken. This interference may induce the methadone metabolism, leading to a consequent fall in plasma concentrations, or inhibit the metabolism, resulting in a rise in plasma concentrations.

Drugs such as protease inhibitors (ritonavir, nelfinavir, indinavir), macrolide antibiotics (erythromycin, clarithromycin), antifungal agents (ketoconazole, itraconazole), serotonergic antidepressants (fluoxetine, fluvoxamine), and grapefruit juice have been implicated in the increase in plasma concentrations of methadone and may induce a prolongation of the QT interval.

4. Other drugs and substances of abuse

A large number of other drugs are directly implicated in the prolongation of the QT interval through an action produced on hERG K⁺ channels. These include commonly prescribed antidepressants (imipramine, amitriptyline, desipramine, sertraline, venlafaxine), antipsychotics (chlorpromazine, haloperidol, risperidone, olanzapine, pimozide, ziprasidone), and antibiotics (clarithromycin, erythromycin) frequently administered to patients undergoing methadone treatment.

It should also be stressed that both cocaine and amphetamines are directly implicated in prolonging the QT interval [15, 19]. Regrettably, this factor lowers the reliability of estimates provided by studies that aim to calculate the prevalence of prolonged QT in subjects undergoing methadone treatment in whom the use of cocaine had not been previously evaluated [2].

5. Physiological and pathological conditions

Additional factors potentially associated with long QT include female gender, age, electrolyte imbalance with hypokalaemia, ischaemic heart disease, heart failure, bradycardia, liver failure, and anorexia nervosa [3, 13, 29].

6. Guidelines

In spite of the discrepancies that emerge from the data obtained from case reports, series of case reports or observational studies, the indications provided, together with the findings of *in vitro* studies, are sufficient to suggest that methadone may be implicated in a dose-dependent manner with prolongation of the QT interval and possible arrhythmic complications.

Therefore, on the basis of the above hypothesis and in line with the proven efficacy of methadone maintenance therapy in the treatment of opioid dependence, an evidence-based support should be made available to clini-

cians to allow them to accurately assess the risk/benefit profile in each individual case.

The first issue to be addressed is whether an ECG is required and which patients should be monitored. Several authors advise that an ECG should be carried out on all patients prior to initiating methadone treatment, to be subsequently repeated after each dose increase. Others argue that ECG should be confined to patients taking high doses of the drug.

Numerous regulatory agencies have published guidelines and recommendations, among which:

- the Medicines and Healthcare Products Regulatory Agency in Great Britain, which was the first authority to propose the monitoring of patients receiving more than 100 mg methadone daily [25];
- the British Drug Misuse and Dependence: UK Guidelines on Clinical Management then incorporated the above approach, recommending that patients be informed of the need for monitoring [8];
- the Canadian Methadone Maintenance Guidelines advise that an ECG be performed in patients taking a dose of over 150 mg per day, to be repeated when dosage reaches the range of 180-200 mg daily [4]. These guidelines suggest that methadone doses should be reduced and the patient sent for cardiological consultation if the QTc interval exceeds 470 milliseconds.

More recently, a panel of experts made up of electrophysiologists, algologists and epidemiologists developed a consensus based on a systematic literature review and discussion of merit, leading to the publication of the following recommendations [18]:

- physicians prescribing methadone should inform patients of the potential risk of arrhythmia;
- physicians should check with patients for any history of heart disease, arrhythmia and syncope;
- ECG should be performed prior to initiating treatment, with a second follow-up to be recorded one month later and annually from then onwards;
- ECG should be performed if methadone doses exceed 100 mg per day or if patients manifest unexplained syncope or convulsions;
- in the presence of a QT interval of over 450 milliseconds, but below 500 milliseconds, the potential risks and benefits of treatment should be discussed with the patient, who should be monitored frequently; if the QTc interval exceeds 500 milliseconds the patient should be advised to suspend methadone treatment or the dose should be decreased; contributing factors such as drugs inducing hypokalaemia should be removed or alternative treatment prescribed;
- physicians should be aware of the interactions

between methadone and other drugs capable of prolonging QT interval or cutting the elimination rate of methadone.

It should be pointed out that the conclusions reached by the panel have been subjected to criticism; they provide no firm evidence that the benefits expected from the ECG screening of all patients who are due to undergo methadone treatment exceed the potential risks associated with failure to perform ECG. Negative aspects of the routine screening of patients are those mainly due to factors associated with redundant examinations, such as anxiety, consequences of false positive recordings, and operational costs. Likewise, the choice of methadone dose in defining the cut-off point for routine ECG screening has been deemed arbitrary [14].

In view of the low prevalence rates estimated for prolongation of the QT interval in the clinical population undergoing methadone treatment (2-5% above 500 milliseconds), it has recently been suggested that ECG screening prior to treatment should be scheduled in patients presenting risk factors including heart disease, family history for congenital long QT syndrome or unexplained sudden death, treatment with CYP P450 system inhibitors, treatment with other drugs capable of prolonging QT interval, HIV infection, use of substances that interact with methadone (benzodiazepines) or those that are directly implicated in QT prolongation (cocaine), and methadone doses exceeding 120 mg. In patients displaying a prolongation of the QT interval and other risk factors, the authors of the above studies have also suggested that the methadone dose be reduced and clinical consequences evaluated or else treatment with other opioids with a long half-life not affecting the QT interval prescribed [2, 13].

The FDA guidelines, currently under clinical investigation, are expected to be published soon [14]. Nevertheless, future measures and recommendations should be based on techniques such as decision analysis, which allow the potential risks and benefits of the procedures mentioned above to be evaluated carefully [14].

6. Conclusions

The finding of a potential risk of prolonged QT is observed in 2-4% of patients on methadone treatment. The risk of torsades de pointes or sudden death is extremely low and is detected in subjects taking exceptionally high doses of methadone or featuring additional risk factors for the onset of cardiac arrhythmias.

For many patients undergoing treatment for opioid dependence, the adoption of a maintenance schedule is a valuable means for managing their condition [5, 11, 24]. The health benefits to be gained from treatment should be closely associated with a careful assessment of the medical aspects involved in long-term treatment.

Despite the diversities reported, the guidelines available to date indicate the need to implement measures that

aim to prevent the risk of QT prolongation in patients on methadone treatment. However, the impact of these measures is limited by the lack of a comparative risk/benefit assessment of specific screening procedures.

Until the results of additional studies may become available, cardiologic assessment (ECG and evaluation of QT interval corrected for heart rate) should be carried out in the presence of risk factors including:

- positive history for long QT syndrome;
- use of drugs or substances of abuse capable of prolonging the QT interval;
- daily methadone dose exceeding 120-150 mg (no scientifically determined threshold is available);
- pathological conditions (electrolyte imbalance, ischemic heart disease, liver failure, etc.).

In these cases all clinical decisions should be taken in line with the findings of ECG recordings and cardiac risk assessment.

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Cardiovascular Complications of Cocaine Use

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Summary

As cocaine use has become prevalent, an increasing number of reports of cocaine-associated morbidity and mortality, largely because of central nervous system and cardiovascular toxicity, appeared. Cardiovascular toxicity is broad, and it may also lead to neurological, psychiatric and other organ-specific symptoms. Cocaine may induce myocardial ischemia by increasing myocardial oxygen demand while simultaneously decreasing myocardial oxygen supply. Most of the cardiovascular toxic effects elicited by cocaine are likely related to its ability to selectively bind to the L-type calcium channels and the potassium channels that modulate the *I_{Kr}* current. In addition, cocaine may promote intracoronary thrombosis in the absence of coronary atherosclerosis. This article briefly reviews the current knowledge regarding the cardiovascular effects of cocaine, providing insight into some of the underpinning mechanisms.

Key Words: adrenergic receptors, monoamine uptake, L-type calcium channels, acute coronary events

In the United States cocaine is, after marijuana, the most often used substance of abuse [4]. It is also the drug of abuse most widely involved in requests for emergency intervention [15]. Approximately 40% of the subjects who visit an emergency department because of a substance-related condition have been using cocaine; of these, 37% are aged between 35 and 44. The number of requests for emergency intervention associated with cocaine use increased by 47% in the period ranging between 1999 and 2002, and is assumed to be on a steady upward path. Cocaine use is the most frequent cause of death correlated with substances of abuse [14]. Forty percent of those who apply to an emergency unit for cocaine-related issues present with chest pain, and 25% of all cases of non-fatal heart attacks in young subjects are associated with cocaine use [8]. The acute and long-term uses of cocaine have both been correlated with a variety of cardiovascular complications: angina pectoris, myocardial infarction, cardiac arrhythmias, acute reversible myocarditis, dilatative cardiomyopathy and sudden death [3, 7, 9]. Moreover, a wide range of cardiovascular complications may develop, involving both large arteries and small vessels and leading to a variety of neurological, psychiatric or other specific organ related symptoms (Table 1) [7, 2]. Despite all these issues, there is a widespread

belief that recreational use of cocaine is safe.

Both cocaine chlorhydrate and free-base cocaine are well absorbed via all transmucosal routes. Peak plasma concentrations and onset of the effects have been recorded in an interval ranging between 30 seconds and 2 minutes after intravenous administration or inhalation; the effects peak about 30 minutes after intranasal administration; when absorption occurs gastrointestinally the peak may come as late as 90 minutes after administration. The duration of effects is proportional to the speed of onset; it is around 15-30 minutes after intravenous administration or inhalation, 1 hour after intranasal administration and up to 3 hours after gastrointestinal absorption.

The risk of acute myocardial infarction is greatest in the 60 minutes that follow cocaine use in subjects with a relatively low risk factor [7]. Myocardial infarction subsequent to use of cocaine is not correlated with the dose taken, its route of administration, or the frequency of use: it has been described at doses ranging between 200 and 2,000 mg, after each of the different routes of administration just indicated, both in habitual and first-time users. Moreover, there is no evidence to suggest that the onset of cardiovascular complications occurs solely in the presence of pre-existing vascular disorders or other conditions [3, 7, 9]. In about 50% of patients

Table 1. Vascular complications of cocaine use	
System	Complications
Central nervous system	Intracerebral hemorrhage, cerebral infarction (stroke), seizures, migraine, vasculitis, blindness
Cardiac system	Coronary vasospasm, heart attack, myocardial infarction, arrhythmias, myocarditis, cardiomyopathy
Aorta and vascular system	Dissection and / or aortic rupture, hypertension
Gastrointestinal system	Mesenteric ischemia and infarction, gastrointestinal perforation, liver failure, splenic infarction
Respiratory system	Pulmonary edema, lung infarction
Musculoskeletal system	Rhabdomyolysis
Cutaneous system	Ischemia
Female reproductive system	Abruptio placentae, miscarriage, prematurity, developmental delays, growth retardation, congenital malformations
Genitourinary system	Renal or testicular infarction myoglobinuria with renal failure

Modificato da: Goldfrank and Hoffman, 1991

affected by cocaine-related myocardial infarction, angiographic examination revealed no signs of atherosclerosis of the coronary arteries. Several autoptic studies have, however, demonstrated the presence of atherosclerotic lesions associated with the formation of thrombi in young cocaine users: thus, cocaine use seems to be correlated with early-onset atherosclerosis and thrombosis. Many of the patients affected by cocaine-related ischaemia or myocardial infarction present with chest pain within one hour of substance use when plasma concentrations of cocaine have risen. Conversely, other patients only report their awareness of chest pain several hours after use, when plasma levels have already fallen or have, at times, become undetectable [3, 7, 8].

Hypotheses put forward to explain the physiopathology of cocaine-related ischaemia or myocardial infarction tend towards a multifactorial pathogenesis in the presence of a condition of stimulation of the central nervous system, cardiovascular system and the respiratory tract. The following factors are involved :

- 1) a higher demand for oxygen (due to an increased heart rate and contractility, and a rise in arterial blood pressure);
- 2) a concomitantly lower or limited myocardial oxygen supply due to vasoconstriction of the coronary arteries;
- 3) a pro-thrombotic condition induced by an increased platelet aggregation and an imbalance between pro- and anti-coagulant factors;

4) an acceleration of atherosclerotic phenomena.

In addition, the positive chronotropic effect produced by cocaine is strengthened by the concomitant use of alcohol. Association with cigarette smoking likewise potentiates the effect of cocaine on heart rate and vasoconstriction, eliciting a greater effect than that induced by cigarette smoke or cocaine alone [3]. This potentiating effect is highly significant, considering the high number of young smokers among cocaine users.

1. Mechanisms underlying the cardiovascular effects of cocaine

Cocaine stimulates the central nervous system, eliciting a state of alert which is itself sufficient to lead to activation of the sympathetic nervous system. Up till the 1970s cocaine-associated cardiovascular complications were explained on the basis of the experimental use of cocaine in distinguishing between direct-acting and indirect-acting sympathomimetic amines. Indirect-acting sympathomimetic amines act at a presynaptic level, as they are transported inside the adrenergic terminals, where they release stored noradrenaline. Cocaine, a membrane transporter inhibitor, when administered immediately prior to tyramine injection, prevents the onset of the cardiovascular effects produced by this classic, indirect-acting monoamine. Noradrenaline, the naturally occurring peripheral sympathomimetic monoamine, prototype of direct-acting amines, is rapidly taken up

by synaptic terminals; this leads to the inhibition of its effects. Cocaine inhibits the re-uptake, or active transport, of monoamines; as a result, its administration potentiates and prolongs the cardiovascular effects of an intravenous injection of noradrenaline. The excessive consequences entailed by central sympathetic activation could be accounted for in this way: inhibition of the re-uptake of the noradrenaline released from sympathetic postganglionic nerve terminals intensify the strengthening of synaptic transmission, leading to severe vascular damage.

The mechanisms underlying cocaine-induced cardiovascular toxicity are actually still more complex than this. Following the advent of tricyclic antidepressants, which display an efficacy comparable with that of cocaine in distinguishing between direct- and indirect-acting monoamines by means of the model outlined above, it soon became clear that these drugs are incapable of potentiating or prolonging the effects of noradrenaline released spontaneously from sympathetic postganglionic nerve terminals. The strengthening effect produced by noradrenaline or other direct-acting amines (noradrenaline transporter substrates) is only expressed at pharmacological doses; the amounts released under physiological conditions undergo rapid dilution, and inhibition of their re-uptake is therefore devoid of any biological relevance. It has since been discovered that preparations made from cardiac tissue or arterial blood vessels respond with greater intensity to specific contractile stimuli in the presence of cocaine when compared with identical untreated preparations. It is generally acknowledged that this sensitization to contractile stimuli is not correlated with sympathetic stimulation mechanisms. Moreover, the clinical use of dihydropyridine calcium antagonists has documented their efficacy in treating many cocaine-related cardiovascular complications. It is likewise a well-established fact that cocaine not only acts as a central stimulant, but also possesses potent local anaesthetic properties.

Local anaesthetics are capable of inhibiting the transport of a stimulus along a nerve or membrane of any type of cell with electrical activity, such as muscle cells. Inhibition is induced by a functional blockade of the voltage-gated sodium channels that are crucial to the distribution and transport of the electric stimulus. Cell membranes expressing various types of ion channels selective for sodium, calcium, potassium, and chloride play an essential role in cell physiology. The effects of a local anaesthetic on these different types of channel may occur in a gradual, selective (dose-dependent) manner. For example, several antiarrhythmic drugs also act as potent local anaesthetics that, when given at low doses (antiarrhythmic doses) bind to the sodium channel during some of its functional phases: they display higher affinity when the channel is activated (open) or inactivated (closed and not activatable), whereas they are rapidly unbound during the resting phase (closed but activatable). Voltage-gated sodium, calcium, and some potassium channels belong to a large family of protein macromolecules with

marked structural similarities; so it is hardly surprising that a local anaesthetic may also display affinity for a calcium or potassium channel. In particular, cocaine is capable of inhibiting sodium, calcium and potassium channels. This capability, however, only applies to local anaesthetic doses that would never be achieved through general use, even during lengthy binges, and would rapidly lead to a fatal outcome. Under specific conditions, it is likely that similar concentrations may be achieved in localized areas, eliciting the onset of arrhythmias or epileptic convulsions (symptoms that may, alternatively, be induced by a vascular spasm accompanied by localized hypoxia). At doses markedly lower than those underlying the blockade of all channels, cocaine is also capable of interfering with L-type calcium channel function (sensitive to calcium antagonists, including dihydropyridines, used in clinical contexts) and a specific potassium channel active in phase 3 (repolarization) of the action potential of cardiomyocytes. This channel determines the I_{kr} current and is targeted both by antiarrhythmic drugs that prolong the action potential, and by drug toxicity that prolongs the QT interval. When low concentrations of cocaine were applied to coronary artery preparations, they produced sensitization to contractile stimuli that were completely antagonized by the presence of nifedipine in the medium [5]. Moreover, cocaine fails to strengthen the action of contractile stimuli that act by releasing calcium from the sarcoplasmic reticular system (from the intracellular reserves) and also fails to activate L-type calcium channels. Coronary arteries express a majority of β -adrenergic receptors and a low number of α -adrenergic receptors on the membrane surface; as a result, synaptic stimulation mainly modulates vasodilation; thus, vasoconstrictor activity exerted by cocaine on coronary arteries is not correlated with stimulation of the synapses. In arterial districts in which the action of α -adrenergic receptors is of an excitatory nature, the sensitizing effects of cocaine to synaptic stimulation, with its many severe implications, is easy to foresee. When applied to an aorta preparation, cocaine potentiated the contractile activity of methoxamine, a direct-acting sympathomimetic amine not susceptible to reuptake by adrenergic terminals [6]; this experiment provided confirmation that the sensitization effect of cocaine is independent of its mechanism of monoaminergic reuptake inhibition.

The myocardium is another key target for these cocaine-elicited effects. L-type calcium channels present on the surface membrane of cardiomyocytes open during the rapid depolarization phase of the action potential (phase 0), so facilitating the slow influx of calcium that characterizes phase 2 (plateau) and are gradually inactivated, preceding to the relaxation phase 3. The probability that these channels will open during the depolarization phase depends on their degree of phosphorylation, with phosphorylated channels being activated at a higher rate. Phosphorylation is mediated by the stimulation of cardiac β_1 -adrenergic receptors. Calcium influx inside

the cardiomyocyte is fundamental in maintaining calcium concentration in the sarcoplasmic reticular system at the levels required by cardiac functions: sympathetic stimulation increases heart rate (as well as the rate of cycles of voltage-gated channel activation), phosphorylates the L-type channels and increases the intracellular calcium reserve. As a result, a greater quantity of calcium is released from the sarcoplasmic reticular system by the contractile apparatus, producing an increase in the contractile strength of the heart. Maintaining a balance between calcium influx, calcium output and the storage capacity of the sarcoplasmic reticular system is of the utmost importance: an excess of intracellular calcium may produce potentially fatal arrhythmias and elicit processes of cell deterioration resulting in apoptosis.

A study performed on isolated ventricular cardiomyocytes demonstrated that cocaine, at concentrations similar to those detected in plasma from recreational users (approx. 1 μM), produces a marked selective increase in currents recorded in voltage-gated L-type calcium channels [13]. The latter effects are rapidly reversible, independent of the degree of phosphorylation of channels and are antagonized by the addition of nifedipine to the medium. Another study conducted on ventricular cardiomyocytes demonstrated how, at a concentration of 4 μM , cocaine prolonged the duration of the action potential as modulated by means of selective inhibition of the I_{Kr} current [1]. In other words, cocaine is capable of prolonging the QT interval with all the negative consequences this may determine.

To conclude, cocaine has shown a proven ability to bind selectively at low concentrations to a specific domain in the L-type calcium channels or potassium channels activated during the repolarization phase in cardiomyocytes that modulate I_{Kr} current. These two actions may explain most of the toxic cardiovascular effects elicited by cocaine. The cardiovascular complications manifested after a single dose of cocaine may be readily explained by a drug-induced state of alert caused by the 'preparatory' action of the sympathetic system and the hypothalamic-pituitary-adrenal axis. A rise in the release of noradrenaline from sympathetic postganglionic nerve terminals determines an increased heart rate, strength of contraction and peripheral vasoconstriction; the increase in peripheral resistance and strength of cardiac contractility is likewise supported by the sensitization of L-type calcium channels and a higher calcium influx into cells at each depolarization. In predisposed tissues or tissue districts, particularly intense vasoconstriction phenomena may be expressed; myocardial hypoxia is associated with repolarization deficits and increase in extracellular potassium that may lead to foci of ectopic depolarization. The increase in the influx of calcium into cardiomyocytes implies a high energy consumption both in terms of increased contractile strength and the activation of the mechanisms involved in its rapid removal from cytoplasm. Hypoxia induces a decrease in ATP

production, promoting the accumulation of intracellular calcium which, if acutely manifested, may elicit the onset of devastating arrhythmias. Autoptic findings obtained from habitual cocaine users have provided indications that chronic calcium accumulation may be implicated in ventricular hypertrophic processes and in the genesis of several morphological alterations, particularly at the level of the contractile apparatus.

It should, in any case, be stressed that the activating action exerted by cocaine on L-type calcium channels is not limited to the cardiovascular system, but has also been implicated in brain neuronal systems to explain complex mechanisms underlying gene activation and synaptic plasticity [10-12]. This mechanism also appears to be involved in the central effects elicited by cocaine. Indeed, the administration of calcium antagonists is not only capable of preventing the onset of severe cardiovascular events, including ventricular fibrillation, but also of interfering with the behavioural and reinforcing effects of cocaine. Moreover, the action on L-type calcium channels may help to explain, at least in part, the increased secretion of adrenaline from the adrenal medulla and various peptide hormones observed following the acute administration of cocaine.

2. Cardiac complications

Cardiac complications including ischaemia and myocardial infarction have been reported both during cocaine intoxication and abstinence. Myocardial infarction was diagnosed in 0.7 to 6% of subjects presenting to an emergency unit for cocaine-associated chest pain; myocardial infarction associated with cocaine use undoubtedly accounts for a significant percentage of the cases that occur at an early age [3, 8]. Heart attacks have been observed in subjects aged between 19 and 40 irrespective of the cocaine dose consumed, and often not associated with convulsions or anxiety. Patients with cocaine-associated myocardial infarction frequently present with: atypical chest pain (usually referred as an 'oppressive' pain), delayed onset of pain that may come hours or days after the last administration of cocaine, or even absence of pain (a study revealed how only 41% of patients reported a sensation of pain prior to hospitalization) [8]. Dyspnoea and diaphoresis are particularly frequent. ECG abnormalities recorded at the time of hospitalization take the form of ST segment elevations and T wave inversions, even if ECG alterations are not found in all patients with acute myocardial infarction [3, 7, 8]. Several studies have demonstrated that the ECG alterations typically observed in the presence of myocardial infarction only affect a small minority of patients. Moreover, the frequency of Q wave and non-Q wave heart attacks is quite similar. High plasma concentrations of troponin and cardiac enzymes are usually detected in both. As emphasized previously, angiographic or autoptic findings obtained from subjects affected by cocaine-associated myocardial infarction

frequently reveal no signs of atherosclerotic lesions or other cardiac disorders. Many patients resume their use of cocaine after discharge from hospital, so determining an extremely high cumulative risk of myocardial infarction and associated complications.

A further potential complication linked to the use of cocaine is the onset of arrhythmias of varying nature: sinus tachycardia, atrial fibrillation, ventricular extrasystoles, onset of idioventricular rhythm, tachycardia or ventricular fibrillation. Besides this, a cocaine-induced ischaemia or myocardial infarction may underlie the onset of arrhythmias that are indistinguishable from atherosclerosis-associated arrhythmias. Experimental animal studies have demonstrated a marked cocaine-induced prolongation of the QRS and QT intervals. These arrhythmias may involve a low level of brain perfusion, with transient loss of consciousness — a frequent occurrence in subjects displaying signs of cocaine intoxication. From a clinical point of view, in a context of cocaine intoxication it is important that a distinction be made between symptoms of cardiac origin and the direct effects produced by cocaine on the central nervous system, particularly in terms of epileptic convulsions or vascular brain spasms.

As the therapeutic strategies applied in the treatment of acute coronary episodes or arrhythmias associated with the use of cocaine differ considerably from those usually employed, when a patient visits an emergency department for chest pain and is examined to confirm the presence of a potential acute coronary syndrome (or arrhythmia), it should first be established whether he or she has recently used cocaine. A pertinent question on this topic should always be asked, especially to young subjects. Urine testing for detection of metabolites should only be performed under specific conditions: for example, when the patient is not capable of communicating and there is no other way of obtaining a reliable patient history.

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