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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 I_{Kr} (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 clinical

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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The author has no relevant conflict of interest to report in relation to the present study.

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