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ORIGINAL ARTICLE

Changes of QTc interval after opioid switching to oral methadone

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Abstract A consecutive sample of patients who were switched from strong opioids to methadone in a period of 1 year was surveyed. QTc was assessed before switching (T0) and after achieving adequate analgesia and an acceptable level of adverse effects (Ts). Twenty-eight of 33 patients were switched to methadone successfully. The mean initial methadone doses at T0 were 67.1 mg/day (SD ±80.2, range 12–390). The mean QTc interval at T0 was 400 ms (SD ±30, range 330–450). The mean QTc interval at Ts (median 5 days) was 430 ms (SD ±26, range 390–500). The difference (7.7 %) was significant ($p<0.0005$). Only two patients had a QTc of 500 ms. No serious arrhythmia was observed. At the linear regression analysis, there was no significant association between mean opioid doses expressed as oral morphine equivalents and QTc at T0 ($p=0.428$), nor between mean methadone doses and QTc at Ts ($p=0.315$). No age differences were found with previous opioid doses ($p=0.917$), methadone doses ($p=0.613$), QTc at T0 ($p=0.173$), QTc at Ts ($p=0.297$), and final opioid–methadone conversion ratio ($p=0.064$). While methadone used for opioids switching seems to be an optimal choice to improve the opioid response in patients poorly responsive to the previous opioid, the possible QTc prolongation should be of concern despite not producing clinical consequences in this group of patients. A larger number of patients should be assessed to quantify the risk of serious arrhythmia.

Keywords Cancer pain · Methadone · QT prolongation · Toxicity · Opioid switching

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Methadone has specific pharmacokinetic and pharmacodynamic properties which could be attractive in several pain conditions. However, dosing of this drug can be challenging for the practicing physicians. Despite lack of reliable equianalgesic conversion ratios, the large interindividual variability in methadone pharmacokinetics, as well as the potential for pharmacological interaction with other drugs, in a selected setting, methadone is an invaluable drug for resolving difficult pain conditions [19]. Early research with methadone-maintained patients revealed that methadone fatalities occur primarily due to respiratory arrest during methadone induction and in the context of polysubstance use. Recent reports of methadone deaths emphasize the role of methadone-related QT prolongation, and the possibility of inducing torsades de pointes, a potentially fatal ventricular arrhythmia [3, 22].

Recent recommendations suggest that methadone should be used by experienced physicians [1]. For these reasons, methadone is commonly used as a second-line drug, for opioid substitution with remarkable advantages from the clinical point of view [17, 18].

The aim of this study was to assess the QTc interval changes in the context of opioid switching, which is the most frequent occasion in daily practice to use methadone in advanced cancer patients unresponsive to previous opioids.

Methods

A consecutive sample of patients who were switched from strong opioids to methadone in a period of 1 year was surveyed. Informed consent and ethical committee approval were obtained. Patients were eligible if they had cancer pain, were receiving opioids in doses of more than 60 mg or oral

morphine equivalents with an unfavorable opioid response, characterized by poor pain control and/or adverse effects, despite symptomatic therapy. Patients with a previous history of arrhythmia or severe bradycardia were excluded. Patients who were receiving potential drugs capable of prolonging QT interval were recorded. The protocol of opioid switching to methadone has been described elsewhere. Shorty, an initial fixed ratio of 5:1 (previous opioid doses expressed as oral morphine equivalents) is used, and then doses are modified on the basis of the clinical response, according to a flexible approach [15, 16]. Patients achieving adequate analgesia and an acceptable level of adverse effects after switching were considered at time of stabilization (Ts) when methadone doses were considered stable and the patient ready to be discharged. Opioid doses and methadone doses were recorded before switching (T0) and at Ts, respectively. To determine the QTc interval, a resting 12-lead electrocardiogram (ECG) was performed at T0 and Ts. The QT interval was corrected for heart rate (QTc) by a computerized system, using the Bazett formula.

Statistics

Data were collected and analyzed by the SPSS Software 14.0 version (SPSS, Inc., Chicago, IL, US) and the Epi Info software, version 3.2.2 (Centers for Disease Control and Prevention). Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all the items. The paired samples Student's *t* test was used to compare parametric variables in the different periods. The comparison between the mean opioid dosages and QTc at T0 and Ts was performed by the simple linear regression analysis. All *P* values were two-sided and *P* values less than 0.05 were considered to indicate statistical significance.

Results

Thirty-three patients were surveyed in the period taken into consideration. Four patients did not achieve dose stabilization and were further switched to other opioids. In one patient, data were incomplete. Twenty-eight patients who were switched to methadone successfully had complete data and were surveyed. The mean age was 63.5 years (SD ±8.1), and 18 were males. The most frequent cancer diagnoses were in a rank order: lung 11 (39.3 %), breast 4 (14.3 %), urogenital 4 (14.3 %), and others 9 (32.1 %). The mean opioid doses at T0 were 310.9 mg/day (SD ±367.1, range 20–1,920), expressed in oral morphine equivalents. The mean initial methadone doses at T0 were 67.1 mg/day (SD ±80.2, range 12–390), with 11 patients (39 %) receiving methadone doses of ≥60 mg/day. The final conversion ratio between the previous opioid, expressed as oral morphine equivalents, and methadone was 5.6 (SD ±3.4, range 1.1–14.0). Ts were achieved within a median of 5 days.

The mean QTc interval at T0 was 400 ms (SD ±30, range 330–450). The mean QTc interval at Ts was 430 ms (SD ±26, range 390–500). The difference (7.7 %) was significant ($p < 0.0005$). Ten male patients had a QTc ≥430 ms after methadone treatment, although two of them previously had a QTc ≥430 ms before switching. No female had any QTc prolongation. Only two patients had a QTc of 500 ms. At the linear regression analysis, there was no significant association between mean opioid doses, expressed as oral morphine equivalents, and QTc at T0 ($p = 0.428$), nor between mean methadone doses and QTc at Ts ($p = 0.315$).

Eleven patients were over 65 years. The mean opioid doses, expressed as oral morphine equivalents, at T0 were 320 mg/day (SD ±234, range 90–900). The mean initial methadone doses at T0 were 57.3 mg/day (SD ±55, range 15–210). The final conversion ratio between oral morphine equivalents of the previous opioid and methadone was 7 (SD ±3.7, range 1.5–14). The mean QTc interval at T0 was 409 ms (SD ±25, range 360–450). The mean QTc interval at Ts was 436 ms (SD ±24, range 420–500). The difference (6.6 %) was significant ($p = 0.015$). No age differences were found with previous opioid doses ($p = 0.917$), methadone doses ($p = 0.613$), QTc at T0 ($p = 0.173$), QTc at Ts ($p = 0.297$), and final opioid–methadone conversion ratio ($p = 0.064$).

Six patients were receiving drugs which potentially prolong QT interval, including haloperidol (two patients), amitriptyline (one patient), doxepin (one patient), ciprofloxacin (one patient), levofloxacin (one patient). The mean QTc interval variations did not differ from those reported in the other patients ($p = 0.1$).

Discussion

An extensive literature search identified over 160 drugs capable of prolonging QT interval [27]. Concerns about a possible association between very high dose methadone and torsades de points have been raised in recent years. A retrospective case series has shown that patients on methadone maintenance treatment who developed torsades de points were receiving mean doses of 397 mg and their mean QTc was 615 ms, although 14 patients had other risk factors for arrhythmia [8]. Since then, a growing body of evidence suggested an association between methadone and QTc prolongation and torsades de pointes in methadone users for maintenance. Many occurred in the setting of additional contributing factors and were associated with relatively high doses of methadone [11]. Proposed threshold for QTc interval prolongation have been set as low as 430 ms for men and 470 ms for women or a gender-independent threshold of 450 ms [11]. By using a modeling and simulation approach, pooled data obtained from

five clinical trials in patients on methadone maintenance treatment reported that with an increase of more than 20 ms or a QTc more than 500 ms, the incidence of torsades de points is expected to increase. Furthermore, methadone doses of more than 120 mg/day can increase the mean QTc interval by 15 ms [4]. However, other than methadone pharmacokinetics, other factors possibly influencing QTc intervals were not examined in this model. How often patients treated with methadone develop arrhythmia is not clear [11], also because prospective data are limited. In a recent cross-sectional study, QTc prolongation prevalence was 18.1 % with no "clinically significant" QTc prolongation of >500 ms or torsades de pointes known to be present [15]. Similarly, while most methadone-treated patients develop QTc prolongation, however, critical QTc prolongation (exceeding 500 ms or increases exceeding 60 ms) occurred infrequently [10].

The mean doses used for chronic pain appears to be much lower than the doses used to treat opioid dependency. In patients with non-malignant pain, minor increases and fluctuations in QTc during a prolonged treatment with methadone in doses of less than 100 mg/day were found [5]. In a mixed population of patients with chronic pain or maintenance therapy receiving methadone with median doses of 110 mg/day, 33 % of patients had QTc prolongation related to methadone dose, but no patient had a QTc longer than 500 ms [2].

Literature on cancer patients is poor. QTc intervals for every ECG performed on and off intravenous methadone therapy in 42 patients receiving mean doses of 408 mg/day, were compared with a separate group of 33 patients treated with mean doses of 235 mg/day of intravenous morphine. The mean differences in QTc intervals on and off methadone were consistent, 41.7 ms, while for morphine was 9 ms. A significant relationship between changes in QTc and methadone dose was found. This finding was attributed to methadone in combination with its preservative chlorobutanol, which produced a synergistic action on cardiac K + current in a separate experimental study performed on human embryonic cells [7]. In a retrospective analysis of 56 available patients receiving median doses of 30 mg/day of methadone, none of them had a QTc >500 ms after methadone therapy [24]. In a more recent study, patients started on methadone for pain management either as initial opioid or as a switch from other opioids was assessed at baseline and the 2 and 4 weeks after. Mean doses were relatively low 2 weeks after (median dose 23 mg/day, range 3–90 mg), and it is likely that most patients were initiated with methadone. At baseline prior to initiation of methadone, 28 % of patients had QTc prolongation. Significant increases in QTc occurred in 1.6 % of patients with no clinical evidence of dangerous arrhythmias [25].

In this study, we recorded the QTc changes of patients who were receiving other opioids unsuccessfully, generally with consistent doses (more than 300 mg/day of oral morphine equivalents on average), and then after patients achieved a clinical stabilization with regular doses of methadone which provided adequate pain relief and symptom intensity, commonly considered as a successful switching. Eleven patients (38 %) received ≥60 mg of methadone/day, which is a relevant dose of methadone (corresponding to 300 mg/day of oral morphine equivalents, according to conversion ratio used), and two patients had QTs values of 500 ms, without any clinical consequence. Of interest, QTc was not related to methadone doses, confirming data recorded in methadone maintenance treatment patients [12, 23, 26], at least in the dose range similar to that reported in this study. This is in contrast with other observations [9, 13, 14]. Indeed, no episodes of arrhythmia were observed. The use of concomitant drugs, potentially influencing the duration of QTc, was uneventful, although the low number of patients cannot allow drawing a definite conclusion.

Drugs with risk of torsades de pointes are divided in three categories: risk, possible risk, and conditional risk. Some of these drugs, such as haloperidol, are commonly given to palliative care patients, for symptom management or to reduce the opioid-related adverse effects, particularly to assist opioid switching, and are rarely discontinued. Of interest, haloperidol, like methadone, belongs to the list of drugs with risk of torsades de pointes, while the other drugs, amitriptyline, doxepin, ciprofloxacin, and levofloxacin are considered as substances with a possible risk [20].

Switching to methadone was effective in most cases and the initial conversion ratio did not change significantly after achieving stable dose, despite the large individual variations. Interestingly, data were similar also in older patients who should be considered at higher risk.

This study has some limitations. Definite conclusion cannot be drawn from a relatively low number of patients. This sample, however, was prospectively assessed in 1 year and reflects the activity of a high volume unit where opioid switching is frequently performed. In a retrospective analysis of medical records of 345 inpatients undergoing opioid switching to methadone no patient presented clinically evident arrhythmias [16]. A single ECG was performed once the patient was receiving stable and effective doses of methadone. While fluctuation of the QT interval found at a stable dose of methadone suggests that a single normal ECG does not guarantee that the patient is not at risk of ventricular arrhythmias [21], no specific timing has been conceived to exclude the risk and any ECG performed at any time would not predict anything [6]. Means of multiple ECG paradoxically could limit the ability of preventing the risk. Patients were re-evaluated about 5 days after switching when the clinical condition was considered optimal and the patients ready to be discharged. From the practical point of view, further analysis in time of QTc was considered difficult. QTc increases seem to be more likely after 6–12 months of methadone therapy [14, 23], so

that the problem could be of interest in cancer patients with prolonged survival.

Expert recommendations suggest performing ECG in patients receiving or starting methadone, particularly, those with multiple risk factors for QT prolongation. These panel recommendations were not intended to supplant clinical judgment and may not apply to patients with difficult cancer pain [11] which is the population examined in this survey. In the broader context of risks and benefits of cancer patients, methadone remains an invaluable drug in the armamentarium of palliative care physicians, and the potential risk should not deter physicians from using it. In any case, patients receiving high dose of opioids unsuccessfully, who require an opioid switching to methadone, are commonly hospitalized to limit the high variability in response to methadone. In conclusion, switching to methadone may produce a QT prolongation and require appropriate monitoring. Clinical consequences as relevant arrhythmia are unlikely in the clinical setting of opioid switching. This data should be confirmed in studies with larger number of patients and in different settings.

Conflict of interest The authors have no conflict of interest to declare.

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