**CASE REPORT**

# ERYTHROMYCIN INDUCED TORSADE DE POINTES IN A METHADONE MAINTENANCE PATIENT: CASE REPORT

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## Abstract

***Objective:*** **This case report highlights the risk of Torsade de Pointes (TdP), a life threatening cardiac arrhythmia in a heroin dependent patient receiving methadone substitution therapy who was prescribed erythromycin for upper respiratory tract infection.** ***Method:*** **We report a case of a 35-year-old Malay man on methadone maintenance treatment who developed TdP possibly due to drug interaction between methadone and erythromycin.** ***Results:*** **The patient reported feeling unwell, chest pain and feeling dizzy after consuming 2 doses of erythromycin. ECG monitoring showed prolonged rate-corrected QT interval leading to TdP. The patient was admitted to the ward where the cardiac arrhythmia ceased following methadone discontinuation. This cardiac arrhythmia was most likely due to drug interaction between methadone and erythromycin (an enzyme inhibitor) which led to an increase in methadone concentration and potentiated the adverse effects.** ***Conclusion:*** **As methadone is a beneficial treatment for heroin dependent patients, the risk of cardiac arrhythmia is of great concern. To avoid complications of drug interaction, patients on methadone therapy should be advised to seek medical assessment before taking other drugs. As TdP is life threatening, it is thus important that physicians and psychiatrists involved in the treatment of heroin dependent patients on methadone substitution therapy be made aware of this risk.** ***ASEAN Journal of Psychiatry, Vol.11 (1): Jan – June 2010: XX XX.***

***Keywords:*** **Methadone, arrhythmia, substitution, Torsade de Pointes (TdP), drug interaction**

## Introduction

Opiate substitution therapy with methadone has been introduced as a pharmacological treatment option for heroin dependent individuals in Malaysia recently [1]. Methadone, approved by the FDA in 1947, has been widely studied and prescribed, and has proven to be an established and effective pharmacological agent to treat heroin

dependent patients worldwide [2]. However, in recent years, the literature has documented cases of methadone associated cardiac arrhythmias [2, 3]. Most of these cases were reported among Caucasians, and thus far there has not been any reported incidence in Malay man. This case report highlights the case of a heroin dependent man on methadone substitution therapy who developed prolonged rate-corrected QT interval (QTc) and Torsade de Pointes (TdP) following concomitant administration of erythromycin.

## Case Report

A 35-year-old Malay man presented to the accident and emergency department complaining of feeling unwell, chest pain and feeling dizzy, but no loss of consciousness. He also had fever and cough for 2 days and had visited his general practitioner who had prescribed erythromycin a day earlier. His fever and cough had subsided, but he complained of the onset of these new symptoms after taking the second dose of erythromycin. A review of his past medical history revealed that he was a previous intravenous heroin user who was attending a community methadone substitution programme for the past 8 months. He was prescribed syrup methadone 110 mg daily and claimed to be responding well to the community opiate substitution programme as he was heroin-free for the last 6 months. He denied any side effect or medical problem since taking methadone. He was not known to have cardiac, respiratory, hepatic or neurological disease. He was also not known to have any major mental health problem. He was married with 2 children and worked as a security guard. He stayed in a rented apartment and smoked 14 cigarettes per day.

Physical examination revealed a conscious but lethargic looking man with normal vital signs and with no cardiovascular, respiratory or neurological abnormalities. Continuous electrocardiogram (ECG) monitoring at the emergency department showed sinus rhythm with a QTc interval of 520 ms (milliseconds) leading to Torsade de Pointes (TdP), but resolved spontaneously. Blood investigations revealed normal blood count and serum electrolytes, normal liver function, normal renal function and normal cardiac enzymes. He was admitted to the cardiac ward for monitoring, prescribed potassium and magnesium supplements, and methadone was discontinued and changed to buprenorphine. The patient's cardiovascular status remained stable and subsequent ECG monitoring after methadone cessation were normal. The patient was discharged with buprenorphine and a follow-up at the cardiology clinic 3 months and 6 months later revealed no further cardiac symptoms with a normal ECG. This case report was written after obtaining informed consent from the patient who agreed with the condition of strict anonymity that may not implicate him.

## Discussion

In recent years, the literature has documented reports of methadone induced cardiac arrhythmias [2-4]. Most of these cases were reported among Caucasian heroin dependent patients, and thus far, the authors are not aware of such incidence in a

Malay man. In this case report, the authors would like to highlight the risk of cardiac arrhythmias, in particular QTc interval prolongation leading to Torsade de Pointes (TdP) in a heroin-dependent patient receiving methadone substitution therapy.

Torsade de Pointes (TdP) has unique ECG characteristics of twisting of the QRS complex around the isoelectric line. It is associated with prolonged QT interval, which may degenerate into sustained ventricular tachycardia and life threatening ventricular fibrillation. Among the known predisposing factors for acquired Torsade de Pointes (TdP) include an underlying cardiac or liver abnormality, electrolyte imbalance (hypokalaemia and hypomagnesaemia) and drugs (methadone, phenothiazines, tricyclic antidepressants and some antibiotics). The mechanism by which methadone induced cardiac arrhythmia was thought to be due to blockade of cardiac K+ channel [2]. As a consequence, the QT interval becomes prolonged and this may precipitate ventricular arrhythmias. In the above patient, the normalization of the ECG following methadone cessation suggests that the Torsade de Pointes (TdP) was most likely caused by methadone as the patient had no other risk factors. A similar finding was also reported in the literature where the QT interval returned to normal within 24 hours following discontinuation of methadone [4].

Methadone is metabolized in the liver by the cytochrome enzyme CYP3A4. Inhibition of the CYP3A4 system may lead to an increase in methadone concentration and cause adverse effects [5]. Some of the known CYP3A4 inhibitors include antibiotics (e.g., fluoroquinolones and macrolides), antihistamines (terfenadine) and psychiatric drugs (e.g., haloperidol and chlorpromazine) (Table 1) [6]. The patient above had consumed erythromycin. Erythromycin, an enzyme inhibitor may have caused an increase in methadone concentration, leading to risk of cardiac blockade and risk of ventricular arrythmias [7]. Furthermore, erythromycin alone has been reported to cause QTc prolongation and provoke TdP, although other macrolides such as clathromycin had lesser risk of TdP but azithromycin did not [8]. The patient above however did not have any major mental health problem and was not on any psychiatric drugs.

Table 1: Examples of psychiatric drugs associated with Torsade de Pointes (this list is not comprehensive) [6]

| |
|---|
| Amitriptyline |
| Nortriptyline |
| Imipramine |
| Desipramine |
| Thioridazine |
| Chlorpromazine |
| Haloperidol |
| Droperidol |
| Clomipramine Maprotiline |
| Doxepin |
| Lithium |
| Chloral hydrate |
| Sertindole |
| Pimozide |
| Ziprasidone |

Cases of methadone induced QTc prolongation and Torsade de Pointes (TdP) were more often reported in patients on high dose methadone above 400 mg daily [2, 3]. It should be noted that the above patient developed ventricular arrhythmia on a lower dose of 110 mg daily. This is probably due to drug interaction between methadone and erythromycin, where the inhibitory effect of erythromycin caused an increase in methadone concentration and thus causing the adverse effects. In the case above, although concern is raised regarding the inhibitory effect of erythromycin in patients receiving methadone, it is also pertinent to mention the potential benefits of the immunomodulatory effects of macrolides for treating pulmonary infections which is commonly encountered in patients receiving methadone maintenance therapy [9].

Although methadone has been reported to induce ventricular arrhythmias, the small risk of Torsade de Pointes (TdP) should not deter physicians or psychiatrists from offering methadone as a treatment option to heroin dependent individuals. In clinical practice, the adverse effects of QT prolonging drugs such as methadone can be prevented by avoiding its use in patients with pre-existing heart disease or risk factors as mentioned above, and/or electrolyte imbalance such as hypokalaemia. It should be emphasized that the risk of cardiac arrhythmia arises with the concurrent presence of other risk factors. Physicians and psychiatrists dealing with patients on methadone therapy should thus be alert to underlying medical diseases that may put patients on methadone at risk of cardiac arrhythmias, be vigilant to the potential of drug interaction between methadone and other drugs and cautious of electrolyte imbalance such as hypokalaemia (diarrhoea or vomiting and use of diuretics). Patients on methadone should be educated to seek medical advice before ingesting other drugs and to seek medical treatment and assessment if they experience chest discomfort, palpitations or dizziness. Part of

the evaluation of these patients should also include an electrocardiogram. In patients who experienced methadone induced arrhythmias, methadone should be stopped and an alternative safer medication such as buprenorphine, which is a partial opioid agonist should be considered. Any adverse event suggestive of cardiac arrhythmias should be reported urgently to drug safety authorities.

Conflict of interest: The authors have given seminars pertaining to methadone and buprenorphine.

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