Itraconazole induced Torsade de Pointes in a patient receiving methadone substitution therapy

M. H. R. Noorzurani, M.Med (Fam Medicine), PhD., [1] Balasingam Vicknasingam, PhD., [2] Suresh Narayanan, PhD. [3]

[1] Associate Professor, Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur,
[2] Senior Lecturer, Centre for Drug Research, Universiti Sains Malaysia, 11800 Penang, Malaysia,
[3] Professor, School of Social Sciences, Universiti Sains Malaysia, 11800 Penang.

Corresponding author**:** Noorzurani, M. H. R., MBBS, M.Med, PhD (Addiction), Associate Professor, Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur. Email: noorzurani@um.edu.my, noorzurani@hotmail.com

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Abstract

Issues: Methadone, a pharmacological agent used to treat heroin dependence is relatively safe, but may cause cardiac arrhythmias in the concurrent presence of other risk factors. **Approach and key findings:** This case report highlights the risk of Torsade de Pointes, a life threatening cardiac arrhythmia, in a heroin dependent patient receiving methadone substitution therapy who was prescribed itraconazole for vaginal thrush. The patient presented to the accident and emergency department for chest discomfort and an episode of syncope following two doses of itraconazole 200mg. ECG monitoring at the accident and emergency department showed prolonged rate-corrected QT interval leading to Torsade de Pointes. The patient was admitted for cardiac monitoring and ECG returned to normal upon discontinuation of methadone. **Implication:** This cardiac arrhythmia was most likely due to drug interaction between methadone and itraconazole because the patient presented with no other risk factors. **Conclusion:** Given the benefits of methadone as a substitution treatment for heroin dependent individuals, the association between methadone and cardiac arrhythmias is of great concern. Physicians treating heroin dependent patients on methadone substitution therapy should, therefore, be cautious of the potential risk of drug interactions which may lead to fatal cardiac arrhythmias.

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Introduction

Methadone, approved by the FDA in 1947, has only been introduced as a treatment option for heroin dependent individuals in Malaysia in the past 3 years [1]. Methadone has been widely studied and prescribed worldwide, and has proven to be an established and effective pharmacological agent to treat heroin dependent patients [2, 3]. However, methadone induced prolonged QTc and Torsade de Pointes have been reported in the literature [4, 5, 6]. More recently, studies of drug interactions involving methadone which resulted in cardiac arrhythmias have also emerged [7, 8], largely among the western population.

This report highlights the first known reported case in Malaysia of a female heroin dependent individual on methadone substitution therapy who developed prolonged rate-corrected QT interval (QTc) and torsade de pointes following concomitant administration of itraconazole.

Case description

A 44-year-old Malay female presented to the accident and emergency department following an episode of chest discomfort and syncope. She had been having itchy whitish curd-like vaginal discharge for 2 weeks and had visited her general practitioner who had prescribed two doses of oral itraconazole 200mg one day earlier. A review of her past medical history showed that she was a previous intravenous heroin user who was

attending a community methadone substitution programme for the past 9 months. She was on syrup methadone 120 mg daily and claimed to be responding well to the community opiate substitution programme as she was heroin-free for the last 4 months. She denied any side effect or medical problems since taking methadone. She was not known to have cardiac, respiratory, hepatic or neurological disease. She was divorced with no children and works as a security guard. She is sexually active, stays in a rented apartment with her partner and smokes 14 cigarettes per day.

Physical examination revealed a conscious but lethargic looking female 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, but resolved spontaneously. Blood investigations revealed normal blood count and serum electrolytes, normal liver function, normal renal function and normal cardiac enzymes. Unfortunately, no analysis of plasma for methadone concentration was done.

She was admitted to the cardiac ward for monitoring, where her methadone was discontinued and changed to buprenorphine, and she was prescribed potassium and magnesium supplements. The patient’s cardiovascular status remained stable and subsequent ECG monitoring after methadone cessation were normal. The patient was discharged on the third day and a follow-up at the cardiology clinic 3 months later revealed no further cardiac symptoms and her ECG was normal.

Discussion

This case report highlights the risk of cardiac arrhythmias, in particular QTc interval prolongation leading to torsade de pointes, due to drug interaction in a Malay female patient receiving methadone substitution therapy.

Torsade de Pointes, a life-threatening ventricular tachycardia has unique ECG characteristics of twisting of the QRS complex around the isoelectric line and associated with prolonged QTc interval, which may degenerate into sustained ventricular tachycardia and ventricular fibrillation [9]. Among the known predisposing factors for acquired torsade de pointes include an underlying cardiac or liver abnormality, electrolyte imbalance (hypokalaemia and hypomagnesaemia) and drugs (methadone, antihistamines, antipsychotics and some antibiotics) [9, 10]. Torsade de Pointes was also more often reported in females [11].

Methadone induced cardiac arrhythmia is thought to be due to the blockade of cardiac K^+ channel. As a consequence, the QTc interval becomes prolonged and this may precipitate ventricular arrhythmias [11]. In the above patient, the normalization of the ECG following methadone cessation suggests that the torsade de pointes was most likely caused by methadone—a finding strengthened by the fact that there was an absence of other underlying factors such as structural heart disease, illicit drugs, other QTc prolonging drugs or hypokalemia. The itraconazole merely acted as a potentiator that increased the serum methadone level and led to further I_{kr} blockade. Walker et al., also

report cases where the QTc interval returned to normal following discontinuation of methadone [7].

Methadone is metabolized in the liver and these processes mainly involve the cytochrome enzymes CYP1A2, CYP2D6 and CYP3A4 [7]. The combination of methadone and a CYP3A4 inhibitor increases the risk of adverse effects [7, 12]. Some of these drugs include the azole antimycotics (ketoconazole and itraconazole), antibiotics (e.g., fluoroquinolones and macrolides), calcium channel antagonists (diltiazem and verapamil) and grapefruit juice [9, 13]. The use of a CYP3A4 inhibitor can decrease drug metabolism both during the first pass and the elimination phases. The decrease in drug elimination may enhance its therapeutic and also its toxic effects.

The proarrythmic capacity of methadone is reported to be mainly dose dependent, where QTc prolongation and torsade de pointes was more often reported in patients on high dose methadone—mean daily dosage 397 mg. [14] However, cases of prolonged QTc interval and torsade de pointes have also been reported over a wide range of dosages including doses that were recommended for addiction treatment [15]. In the above patient, ventricular arrhythmia developed on a lower dose of 120 mg daily.

Methadone is relatively safe when prescribed within recommended doses and with full monitoring by health personnel and the small risk of torsade de pointes should not deter physicians from offering it as a treatment option to heroin dependent individuals. The risk of arrhythmia only arises with the concurrent presence of other risk factors such as

existing cardiac or liver disease and potential interaction between methadone and other drugs such as antimycotics and antibiotics. Extra caution is also warranted in situations that cause hypokalaemia such as diarrhoea or vomiting and use of diuretics. Pre-treatment electrocardiogram (ECG) screening is recommended in such cases [11, 15, 16]. More specific guidelines in the literature call for pre-treatment ECG to measure the QTc interval to be followed up by another within 30 days and annually thereafter. Additional ECG is indicated if methadone doses exceed 100mg/day or if unexplained syncope/ seizures are present [11]. 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. In patients who experienced methadone induced arrhythmias, an alternative safer medication such as buprenorphine, which is a partial opioid agonist should be offered. Buprenorphine is a less potent I_{kr} blocker [17] and therefore has a better safety profile. The lower risk of QTc prolongation with buprenorphine is well supported by clinical studies [18, 19, 20].

Conflict of interest: The first and second authors have been invited to give seminars on drug addiction sponsored by Schering Plough (M) Sdn Bhd.

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