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Case Report Open Access

Poly Pharmacy-Induced Long-QT Syndrome and Torsades de Pointes: A Case Report

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Abstract

Polypharmacy-induced QT prolongation is a possible hazardous adverse effect of several medication combinations. When QT prolongation leads to torsade de pointes, life-threatening or mortal outcomes can result. A 45-year-old man presented to the emergency department due to the use of methadone in the field with ventricular tachycardia and after successful resuscitation after cardiac arrest, under ICU care, has been exacerbated torsade de point due to polypharmacy with high-dose methadone, the patient had multiple risk factors for prolonged QT syndrome including methadone therapy, multiple drug therapy leading to potential drug interactions, electrolyte disturbances such as hypomagnesaemia. Clinical pharmacy must be aware of multidrug interactions potentiating QT prolongation and leading to torsade de pointes. In this article has emphasized the importance of considering the cumulative effects of several drugs used in the ICU and their timely treatment and possible avoidance of poly pharmacy.

Keywords: Torsades de pointes; Drug induced; Polypharmacy, ICU

Introduction

Case report

A 45 year-old man was admitted to the emergency department due to cardiorespiratory arrest during sleep. Laboratory results showed methadone urine test positive, serum chemistries with serum level of magnesium 1.7 mg/ml, other toxicological values were in normal range. A review of his past drug history revealed that he was a prescribed syrup methadone 120 cc daily equivalent 625 mg, on the day of the incident he was a concomitant usage of amphetamine and cigarette with methadone. His echocardiogram demonstrated an EF=35%.

After cardiopulmonary resuscitation and return to spontaneous circulation, he was admitted in intensive care unit. The primary diagnosis was hypoxic ischemic encephalopathy. During ICU stay, his hemodynamic was stable, GCS +6, no sign of brain hypoxia and mydriatic pupillary response and both eyes respond normally to light. Over the first few days of his hospitalization, he had several episodes of ventricular tachycardia which leads to hypotension that eliminated by cardio version on its interval his ECG showed sinus rhythm, with frequent multifocal premature ventricular complexes which leads to atrial flutter that resolved with IV amiodarone and propranolol after amiodarone protocol, he was given oral amiodarone.

For management of opioid dependence, he was given methadone syrup through gavage feeding tube and methadone dosage increased up to 125 cc syrup, hypomagnesaemia was corrected via 3 grams magnesium sulfate intravenous infusion and propofol infusion was tapered.

To prevent methadone toxicity, 0.2 mg oral clonidine BD was added. After extubation, propofol was discontinued then midazolam was administered 2 milligrams PRN.

Several days later, the patient became symptomatic, frequently episodes of ventricular tachycardia occur, which recognized as drug induced QT prolongation and torsades de pointes. Due to hemodynamic instability, prompt defibrillation and intravenous magnesium sulfate were administered. Potassium levels preserved in the high normal range and all pharmacologic offender agents were immediately discontinued.

QT-prolonging drugs such as Citalopram, aminophylline, Clonidine and chlorpromazine were discontinued, over the 10 days, ventricular tachycardia was control, patients moved quickly into full consciousness and uncomplicated brain, he was introduced into the Electrophysiology clinic to continue treatment.

Discussion

Polypharmacy is determined as the concurrent use of several medications and/or the administration of multiple drugs, which is common among the hospitalized patients, is associated with factors such as number and severity of illnesses, number of physicians seen, type of drugs used, which is a well-known risk factor for adverse drug reactions a well-known risk factor for adverse drug reactions. polymedications sometimes lead to unpredictable interactions with a range of problems in older patients especially when several drugs are used to treat different conditions [1].

Drug interactions are seen in 80% of people taking more than 5 concurrent drugs. patients taking 5 concurrent medicines have a 50% risk of at least one drug interaction, each additional medicine adds a 12% increase [2] adverse reactions due to polypills, may also be misinterpreted as a medical condition and lead to the prescription of additional medications. Identifying the risks of multiple medications is

an important first step but does not always predict functional or adverse outcomes.

Torsadesde pointe is a polymorphic ventricular tachycardia which can rapidly evolve into ventricular fibrillation and death abruptly. Many factors may cause prolonged or abnormal duration of the action potential mainly by delaying the repolarization phase 3 which is associated with TdP. Patients with torsade de pointes, have risk factors that can be easily identified from the medical history and clinical evaluation before the initiation of new drugs [3]. Some of the "easily identifiable risk factors" consist of, female gender, heart disease, determined by MI, heart failure and valve-cardiomyopathy, myocardium heterogeneity, electrolyte disturbances especially hypokalemia (potassium serum levels 3.5 meq/L), genetic polymorphism, drug toxicity due to impaired drug metabolism for kidney or liver deficiency, elderly patients, a family history of long QT syndrome, a prior history of drug-induced torsade, or a prolonged QT interval [4], possible drug interactions associated with the administration of two or more drugs that prolong the QT interval or challenge for the same metabolic pathway, drug induced QT prolongation e.g anti arrhythmic drug (Quinidine, Procainamide, Flecainide, Amiodarone, Sotalol), psychiatric drugs (Thioridazine, Chlorpromazine, Haloperidol, Imipramine, Maprotiline, Doxepin, Lithium), antihistamines (Terfenadine, Diphenhydramine), antimicrobial and antimalarial drugs (Erythromycin, Clarithromycin, Chloroquine), serotonin agonists/antagonists (Cisapride), immunosuppressant (Tacrolimus), antidiuretic hormone (Vasopressin), other agents (Cocaine, Papaverine) [5]. The most common stimulating drugs are anti dysrhythmics and psychiatric medicine [6].

QT prolongation mostly contains combinations of antihistamines and macrolide or imidazole antibiotics, concurrent use of more than one QT-prolonging antipsychotic drug, Cisapride and Erythromycin, and antimicrobial agent (Macrolides or Quinolones) with anti arrhythmic drugs. Recent Quinolones, new antipsychotic drug that represented very clinical efficacy during clinical trials were recently recede from the market when their potential for QT prolongation and pro arrhythmia was understand [7] this arrhythmia mostly occurs secondary to drug-induced cardiac repolarization dysfunction typically results from the development of early after depolarization and triggered activities from prolonged repolarization. many drugs can prepare condition to this fetal tachycardia [8] class III anti arrhythmic drugs, which prolong repolarization and cardiac refractoriness, non-cardiac drugs (Haloperidol, Methadone in this case) have been recognized to delay cardiac repolarization and to share the ability with class III anti arrhythmic to cause TdP occasionally. A diversity of several K^+ channel subtypes are existing in the heart. Two significant K^+ currents participating in ventricular repolarization are the subtypes of the delayed rectifier current, IKr and IKs. The action potential may prolong with blockage these potassium currents. The blockade of IKr current by some medications is at least in part responsible for their pro-arrhythmic effect. Blockade of the IKr current causes T or U wave abnormalities on the surface ECG and prolonged QT interval. Sometimes subsequent activation of an inward depolarisation current, known as an early after depolarization makes prolongation of repolarization. when accompanied by the attendance of a remarkable increased dispersion of repolarization, this could induce re-entry and provoke TdP, which is then sustained by further re-entry or spiral wave activity [5]. Plenty of drugs with no cardiac indications such as many antibiotics, antipsychotic medicines or antihistamines, block the same cardiac potassium channels so could lead to QT prolongation and torsade de pointes [9]. Several drugs had been subject of withdrawal because QT-prolongation and arrhythmia [10]. QTc prolongation has before been reported in patient using methadone maintenance therapy [11]. Methadone delays cardiac repolarization as a potent blocker rapid component of potassium ion current (Ikr) potassium channels, it is independently correlated with a prolonged corrected QT (QTc) interval and increased risk of torsades de pointes (TdP) [12]. one case study reports occurrence of a significant typical QT prolongation, after administration of macrolide antibiotics, Azithromycin, particularly in the context of co administered medications that inhibit the cytochrome P450 (CYP) 3A4 isoenzyme, as ketoconazole [13] Flecainide, a class IC drug, also represents inhibitory actions on the K(+) channels, causing QT interval prolongation. a studyrecognizes six cases of Flecainide-induced TDP, bradycardia was present in all cases, two arrhythmias caused by Flecainide: [14] another case study presented a 41-year-old woman who developed torsade de pointes 55 minutes after 80 mg haloperidol IV, the nto control the arrhythmia magnesium sulfate 2 g/100 mL NaCl 0.9% was administered, [15] another study considered QTc prolongation was similar for Quetiapine and Haloperidol (another antipsychotic associated with QTc prolongation) ICU patients are at much high risk of QTc prolongation and quetiapine use in ICU patients should be very prudent. similarly, patients with delirium or numerous acute medical problems would be at risk of QTc prolongation either due to existing risk factors [16] Haloperidol induced TdP especially in combination with electrolyte disturbances, hypokalemia and hypomagnesemia which were contributing factors for QTc prolongation [17] many systematic studiespresent the risk factors for developing QT interval prolongation and TdP in patients, hypokalemia and heart diseases were respectively reported in 28% and 41% of patients, drug interactions associated with the administration of polymedications prolonging the QT interval were present in 39% of patients, in patients at risk, who has already presented with QT interval prolongation and who should use a drug with arrhythmic potential, or those receiving many medications for life-saving indications, ECG monitoring might be considered [18] patients with uncorrected hypokalaemia or hypomagnesaemia that taking amiodaroneor other antiarrhythmic agents are in risk of arrhythmia [19].

In one case report An 80-year-old man took levofloxacin IV, this case became pulseless and loss of consciousness and ventricular arrhythmia matchable with torsades de pointes was found. Fluoroquinolones should still be used with caution in individuals with risk factors for QT prolongation [20]. In one case study which focus on managing polypharmacy in the elderly, it was seen based on using of more drugs and age-related pharmacokinetic and pharmacodynamic changes, the risks of toxic drug reaction and adverse medicines event are augmenting in elderly patients [21], other study shows the stringent occurrence of medicine induced TdP in the general population is often unknown. Most of our conception of the incidence, risk factors, and medicine interaction of pro-arrhythmic drugs are taken form studies, case reports, clinical studies during drug development, and post-marketing surveillance [5]. the mechanisms of this potentially fatal phenomenon is related to many drugs which lengthen QTc (QTc interval is greater than 440 ms (men) and 460 ms (women) and cause TdP, generally via their blocking of the potassium channel IKr, some drugs prolong QTc in a dose-dependent manner, others do so at any dose and it is significant to identify that drugs interacting with the metabolism of a QT-prolonging drug could result in higher plasma concentrations and therewith rise the risk of arrhythmia. many are metabolized by the cytochrome P450 iso enzyme

CYP3A4. Poly pharmacy with other drugs utilizing the same enzyme, or inhibiting CYP3A4, can lead to TdP [22]. QT prolonging drugs and medicines interfering with their metabolism should be immediately discontinued.

For prevention of Polypharmacy induced QT prolongation, avoiding delinquent drugs use in patients with pre-existing heart disease or risk factors as mentioned already, prior ventricular arrhythmias, and/or electrolyte imbalance particularly hypokalaemia. Co-administration of medicines that inhibit the cytochrome P450 (for example, imidazole antifungals, macrolide antibiotics) or those that can prolong the QT interval or drugs that cause electrolyte imbalance should be avoided, the serum potassium concentration should be checked orderly as a matter of routine care when the patient is on potassium wasting diuretics. As well as, it may be sound clinical practice to perform ECGs usually before and after an initiation or increase of dosage of a drug that may prolong the QT interval. If the patient develops TdP, the offending drug should be stopped and electrolyte abnormalities corrected. Medications that can prolong the QT interval must preferablybe listed. Any adverse event suggestive of cardiac arrhythmias should be reported [5].

Treatment for TdP includes immediate defibrillation for hemodynamic instability infusing intravenous magnesium (1-2 g bolus followed by an infusion of 2-4 mg/minute) is the initial therapy of choice irregardless of serum level. Serum potassium should be maintained in the high-normal range (4.5-5 mmol/L). Temporary cardiac pacing could be needed to rise the heart rate and shorten the QT interval, short-term pacing rates of 90 to 110 beats/min are usually used. experience with permanent pacemakers suggests rates >70 beats/min protect against drug-induced TdP. If temporary pacing is unavailable or while preparing for intravenous catheter insertion, isoproterenol, titrated to a heart rate ≥ 90, is useful but it is contraindicated in patients with prolongation of the QT interval at basal ECG or ischemic heart disease. Long-term treatment involves avoidance of culprit agents. Electrolyte imbalance must be corrected. In patients with sick sinus syndrome or atrioventricular block and bradycardia or pause-dependent medicine-induced arrhythmia, permanent pacing with programmable pause prevention algorithms may be indicated [22]. We should carefully consider the risks *vs.* benefits of these factors, particularly when prescribing them to elderly patients, to those who have multiple comorbidities, or to those who are taking multiple medications.

Conclusion

Polypharmacy leads to a high risk of adverse effects. Accordingly, it is crucial to recognize patients receiving medicines that can induce QT interval prolongation and accomplish serial electrocardiograms, due to the possible risk of ventricular arrhythmias. methadone-induced TdP is a potentially mortal complication of methadone therapy. As the generality of methadone use raises, we incidence more ICU cases of methadone and polypharmacy induced TdP, Hence, a thorough patient history and electrocardiogram monitoring are necessary for patients treated with several drugs. Due to the unpredictable nature of QTc prolongation and TdP, we should be alert of how to monitor these drugs and to prevent posibility mortal arrhythmias. Periodic ECG monitoring of the QTc interval and discontinuation of various drugs in the setting of prolonged intervals is ideal. Electrolyte disturbances particularly hypokalemia, should be immediately corrected. In the case of patients with severe opioid dependency requiring, very high doses of methadone, alternative safer agents such as buprenorphine, a partial opioid antagonist/agonist, Finally, we able to control repeated attacks of TdP with reduced methadone dose, deleted polypharmacy and other triggers and induced sedation and extubate patient. Our aim in this case report was to highlight the hazard of cardiac arrhythmias, especially QTc interval prolongation leading to TdP in a patient receiving multiple drug therapy, and then to present a sight on treatment and prevention methods of polypharmacy induced prolonged QTc. At the end in patient who experienced drugs induced arrhythmias, consideration of cumulative action of several drugs adverse effects which used in ICU, needed to quick management and if possible abstinence of several medications therapy.

References

1. Aronson J (2004) In defence of polypharmacy. Br J Clin Pharmacol 57: 119-120.
2. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C (2013) Prevalence and risk of potential cytochrome p450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. Ann Pharmacother 47: 324-332.
3. Smalley W, Shatin D, Wysowski DK, Gurwitz J, Andrade SE, et al. (2000) Contraindicated use of cisapride: impact of food and drug administration regulatory action. Jama 284: 3036-3039.
4. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, et al. (2003) Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine 82: 282-290.
5. Yap YG, Camm AJ (2003) Drug induced QT prolongation and torsades de pointes. Heart 89: 1363-1372.
6. Prosser JM, Mills A, Rhim ES, Perrone J (2008) Torsade de pointes caused by polypharmacy and substance abuse in a patient with human immunodeficiency virus. Int J of Emerg Med 1: 217-220.
7. Commission FD (1999) FDA/PhRMA task force to assess QT risk by pre-clinical markers. Pink sheet 61: 15-16.
8. Russell L, Levine D (2013) Methadone-induced Torsades de pointes. R I Med J 96: 20-21.
9. Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM, et al. (2004) Drug-Induced torsades de pointes and implications for drug development. J cardiovasc electrophysiol 15: 475-495.
10. Ponte ML, Keller GA, Di Girolamo G (2010) Mechanisms of drug induced QT interval prolongation. Curr drug saf 5: 44-53.
11. Vieweg WVR, Hasnain M, Howland RH, Clausen T, Koneru JN, et al. (2013) Methadone, QTc interval prolongation and torsade de pointes: Case reports offer the best understanding of this problem. Ther Adv Psychopharmacol 3: 219-232.
12. Khalesi S, Shemirani H, Dehghani-Tafti F (2014) Methadone induced torsades de pointes and ventricular fibrillation: A case review. ARYA Atheroscler 10: 339-342.
13. Huang BH, Wu CH, Hsia CP, Yin Chen C (2007) Azithromycin-induced torsade de pointes. Pacing Clin Electrophysiol 30: 1579-1582.
14. Nasser M, Idris S, Marinelli K, Machado C (2015) Flecainide-induced Torsades de Pointes: Case Report and Review of Literature. Rev Cardiovasc Med 16: 214-220.
15. O'Brien JM, Rockwood RP, Suh KI (1999) Haloperidol-induced torsade de pointes. Ann pharmacother 33: 1046-50.
16. Hasnain M, Vieweg WVR, Howland RH, Kogut C, Breden Crouse EL, et al. (2014) Quetiapine, QTc interval prolongation, and torsade de pointes: a review of case reports. Ther Adv Psychopharmacol 4: 130-138.
17. Ayad RF, Assar MD, Simpson L, Garner JB, Schussler JM (2010) Causes and management of drug-induced long QT syndrome. Proc (Bayl Univ Med Cent) 23: 250-255.
18. Abriel H, Schlapfer J, Keller DI, Gavillet B, Buclin T, et al. (2004) Molecular and clinical determinants of drug-induced long QT syndrome: an iatrogenic channelopathy. Swiss med wkly 134: 685-694.

19. Stahlmann R, Lode H (2003) Fluoroquinolones in the elderly: safety considerations. Drugs Aging 20: 289-302.

20. Letsas KP, Efremidis M, Kounas SP, Pappas LK, Gavrielatos G, et al. (2009) Clinical characteristics of patients with drug-induced QT interval prolongation and torsade de pointes: identification of risk factors. Clin Res Cardiol 98: 208-212.

21. Bennis Nechba R, El M'barki Kadiri M, Bennani-Ziatni M, Zeggwagh AA, Mesfioui A (2015) Difficulty in managing polypharmacy in the elderly: Case report and review of the literature. J Clin Gerontol Geriat 6: 30-33.

22. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG (2007) Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 153: 891-899.