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 multdrug 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 polypharmacy.

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

Introduction

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 cardioversion 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 polypharmacy, 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.

Torsades de 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, Flecaainide, Amiodaron, Sotalol), psychiatric drugs (Thioridizane, Chlorpromazine, Haloperidol, Imipramine, Maprotoline, Dopenex, Lithium), antiarrhythmics (Teferadine, Diphenhydramine), antimicrobial and antimalarial drugs (Erythromycin, Clarithromycin, Chloroquine), serotonin agonists/antagonists (Cisapride), immunosuppressant (Tacrolimus), antiiduretic 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 antiarrhythmics 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 determined by MI, heart failure and valve-cardiomyopathy, 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, Flecaainide, Amiodaron, Sotalol), psychiatric drugs (Thioridizane, Chlorpromazine, Haloperidol, Imipramine, Maproteline, Dopenex, Lithium), antiarrhythmics (Teferadine, Diphenhydramine), antimicrobial and antimalarial drugs (Erythromycin, Clarithromycin, Chloroquine), serotonin agonists/antagonists (Cisapride), immunosuppressant (Tacrolimus), antiiduretic hormone (Vasopressin), other agents (Cocaine, Papaverine) [5]. The most common stimulating drugs are anti dysrhythmics and psychiatric medicine [6].
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 hypokalemia. 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 preferably be 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 (4.5-5.5 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 ativoventricular 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 possibility 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


