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CASE REPORT

After more than 300 defibrillation shocks, patient still alive 12 years later refractory torsade de pointes due to polypharmacy and persistent vomiting

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Abstract Acquired torsade de pointes ventricular tachycardia (TdP) is a rare but serious life-threatening arrhythmia caused by an array of cardiac and non-cardiac drugs. It is often refractory to pharmacological therapy and may result in death or require frequent defibrillations. In our case study a young female patient with no underlying heart disease developed very frequent sustained TdP requiring frequent defibrillations without which she would have certainly died. The ventricular arrhythmia in this patient was of multifactorial origin – cisapride, drug–drug interaction and persistent vomiting resulting in electrolyte disturbance and malnutrition. The patient survived after more than 300 defibrillation shocks over a period of 5 days and she is still alive 12 years later.
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1. Introduction

Polypharmacy is often unavoidable in patients with multiple problems. However the treating physician must be aware of the risks and be vigilant for complications especially ventricular arrhythmias which may be fatal. Every effort to avoid drug–drug interaction in a high risk patient should be made, but if TdP occurs, proper persistent management may be effective and life saving. This brief report is about a young female who developed refractory and frequent TdP as a result of vomiting and polypharmacy. She was successfully treated by correcting her electrolyte disturbance and stopping the offending drug which in our case was cisapride.

2. The case

This is a 36-year old lady who is Para 5 + 2, had Caesarean section on October 24, 1998. Due to uncontrollable uterine bleeding hysterectomy had to be done. She presented on November 18, 1998 to ER complaining of abdominal pain, fever, nausea and vomiting of 3 days duration. Physical examination showed heart rate: 106 bpm, BP: 120/70 mmHg, and temperature: 37.9 °C. A tender supra-pubic mass 10 × 10 cm

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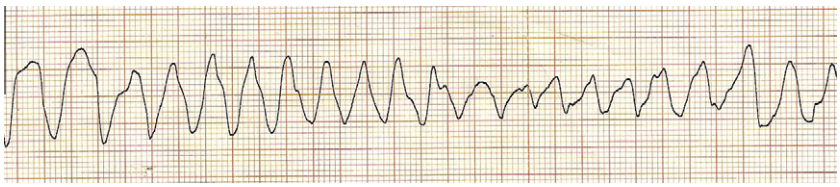

Figure 1 ECG tracing representing classical Torsades de pointes pattern at ventricular rate of approximately 210 beat per minute.

was observed. The rest of the examination was unremarkable. Electrocardiogram showed sinus tachycardia with QTc (Bazett formula) of 440 ms. Investigation showed Hgb 9.7 g/dl MCV 79, WBC 7.0 k/μl, serum albumin 3.1 g/dl K 3.9 meq/L corrected Ca 7.9 mg/dl. Patient was admitted to OB/GYN service with impression of infected rectus sheath hematoma. The patient was started on loperamide, metronidazole, nitrofurantoin and later trimethoprim/sulfamethoxazole and tetracycline were added after culture and sensitivity results. Patient continued to have severe nausea vomiting and anorexia despite all trial of anti-emetics including metoclopromide and ondansetron. Upper GI endoscopy on December 1, 1998 revealed non-ulcer dyspepsia and GERD. Ranitidine 150 mg po bid, and cisapride 10 mg tid were added. Two days later on December 3, 1998, she collapsed and became unconscious and pulseless. Found to have ventricular tachycardia (Fig. 1) which responded to defibrillation. The patient was put on mechanical ventilation and shifted to ICU. ECG showed prolonged QTc measuring 630 ms. Serum K 3.2 meq/L, Mg 1.6 mg/dl which were corrected by intravenous $MgSO_4$ for a total dose 5 g and KCl 40 meq/L at 100 cc/h during her stay in the ICU. The patient continued to have frequent TdP requiring 50–70 defibrillation shocks per day. Several anti-arrhythmic agents including bretylium, phenytoin, isoprenaline, amiodarone, lidocaine and $MgSO_4$ were tried without any response. On December 7 cisapride was discontinued as a possible cause of this patient's arrhythmia. The patient's last episode of TdP occurred on December 8, 1998. The vomiting also ceased. On December 15 she was transferred to the female medical ward and discharged the next day from the hospital. The patient never came for cardiology follow up. Her hospital file showed she was last seen in ER on September 30, 2008 for gastroenteritis.

3. Discussion

Cisapride, a gastrointestinal prokinetic agent, is known to prolong the QT interval and lead to life-threatening TdP. In 1995 the first case of ventricular arrhythmia linked to cisapride was reported to the FDA (Janssen Pharmaceutica, 2000). By 1999, the FDA received 117 report of patient developed QT prolongation; 107, torsades de pointes; 16, polymorphic ventricular tachycardia; 18, ventricular fibrillation; 27, ventricular tachycardia; 25, cardiac arrest; 16, serious (unspecified) arrhythmia; and 15, sudden death; for a total of 341 individual patients affected following use of cisapride of which 80 (23%) died (Diane et al., 2001). By year 2000 cisapride was withdrawn from the US market (Diane et al., 2001). Cisapride was further studied and it was found to be associated with doubling to tripling of the risk of hospitalization for ventricular arrhythmias and eightfold risk in the initial prescription period (Hennessy et al., 2008).

Inhibitors of CYP3A4 like macrolides, midazolam, verapamil, etc., may interfere with metabolism of cisapride and therefore, associated with increased risk of ventricular arrhythmias (Gupta et al., 2007). Mechanism of drug induced QT prolongation and TdP is explained by the fact that the myocardial repolarization is primarily mediated by efflux of potassium ions. Two subtypes of the delayed rectifier K + current, Ikr (rapid) and Iks (slow), are predominantly responsible for repolarization. Virtually all drugs that prolong QTc block Ikr (Mitcheson et al., 2000).

A more recent study conducted on canine was able to demonstrate the effect of cisapride on QT interval and induction of TdP (Di Diego et al., 2003).

Recommended modalities of treatment in drug induced TdP include intravenous magnesium sulfate as an initial therapy of choice regardless of serum level (Banai and Tzivoni, 1993). If sustained hemodynamically unstable polymorphic ventricular tachycardia or VF develops, immediate nonsynchronized defibrillation is indicated. Serum potassium should be maintained in the high-normal range (4.5–5 mmol/L). Simultaneous use of other QT prolonging drugs must be avoided; likewise medications likely to interfere with their metabolism must be promptly discontinued. Overdrive transvenous pacing shortens QTc and is highly effective in preventing recurrence (Khan, 2002).

In our case TdP might not be solely due to drug induced QT interval prolongation. Eating disorders including anorexia nervosa, bulimia and binging and purging are known to cause QT prolongation (Takimoto, 2004). Bulimia nervosa is a primarily psychological disorder but the QT interval prolongation is mainly due to the metabolic derangements associated with repeated vomiting. Hypokalemia, hypochloremia and metabolic alkalosis were observed (Mitchell et al., 1983).

In our case we felt that cardiac effect of repeated vomiting was a significant contributory factor similar to what happens in bulimia nervosa. It is safe to conclude that it was of multifactorial origin including cisapride, drug–drug interaction which affected metabolism of cisapride by inhibition of CYP3A4 (metronidazole, ranitidine, and amiodarone) and electrolyte disturbances resulting from repeated vomiting and poor nutritional intake.

Despite trial of many anti-arrhythmic agents she continued having frequent episodes of sustained TdP requiring at times more than 100 defibrillation shocks in a day. The persistence of the team paid of and the patient recovered and was discharged in a good condition.

4. Conclusion

Drug induced torsade de pointes is a very serious arrhythmia and physicians must be specially watchful for this complication in high risk patients on certain drugs known to cause QTc pro-

longation. Female sex, malnutrition, electrolyte disturbance and polypharmacy are known risk factors for torsade de pointes. The arrhythmia is life threatening and most drug related fatalities are due to this proarrhythmic effect. These patients should be managed aggressively paying special attention to immediately stopping the culprit drug and magnesium administration and correcting all the risk factors.

It is very critical to identify the possible cause(s) of the arrhythmia since elimination of the cause is essential. Persistent vomiting might have cardiac complication similar to that of bulimia nervosa, however, further studies are needed to establish such association. We advice a careful approach for patient on polypharmacy and metabolic disturbances. The fact that after more than 300 defibrillation shocks the patient is still alive more than 12 years later, emphasizes that the treating physician must be perseverant in managing drug induced torsade de pointes since it is a potentially correctable arrhythmia.

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