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Case Report

Ciprofloxacin induced acquired long QT syndrome

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Abstract: Quinolone antibiotics have potentially serious proarrhythmic effects. The effects on intracardiac potassium channels result in QT interval prolongation, leading to torsades de pointes. Evidence suggests fluoroquinolones cause QT-mediated proarrhythmia, and weak evidence links ciprofloxacin with QT-mediated arrhythmias. Ciprofloxacin may be given to select patients because the agent is believed to be safer than other drugs in its class. We report a case of ciprofloxacin-induced Q-T prolongation in a 33 year-old woman within 48 hours of its administration.

Keywords: Ciprofloxacin, Quinolones, QTc prolongation, Proarrhythmia, Toxicity.

INTRODUCTION

The explosion of knowledge in the field of genetics has provided new insight into the development of cardiovascular disease. Disease, as a process of the interaction between genes and environmental factors, has been a focus of research. Acquired long QT syndrome (LQTS) is a recognized cardiovascular problem that can precipitate torsade de pointes (TdP), a potentially fatal arrhythmia. Acquired LQTS probably occurs as a result of the interaction between an environmental factor and the genes that encode for the process of myocardial excitation and recovery. Common environmental factors associated with this disorder are drugs, drug-drug interactions, and electrolyte imbalances (Kunkler, K. 2002).

Quinolone antibiotics are frequently prescribed agents with a broad spectrum of antimicrobial efficacy. Several quinolones associated with recognized QT prolongation, including sparfloxacin and grepafloxacin, have been voluntarily withdrawn from the market by the manufacturer due to concerns about QT-mediated arrhythmias. Ciprofloxacin is often chosen when there is concern about QT interval mediated arrhythmias; because of its weak clinical link to QT prolongation and torsade de pointes (Kunkler, K. 2002; Patmore, L. *et al.*, 2000; Bischoff, U. *et al.*, 2000; Adamantidis, M. M. *et al.*, 1998 ; & Chiba, K. *et al.*, 2004).

To increase the awareness of this life-threatening phenomenon we report an illustrative case in which acquired prolongation of the QT interval due to electrolyte derangement and administration of ciprofloxacin resulted in cardiac arrest due to ventricular tachycardia.

CASE REPORT

A 33 year old woman presented to the emergency complaining of dyspnea, productive cough with greenish sputum and fever accompanied by general malaise for one week, complicated by orthopnea 12 hours before admission .There was no associated nausea or vomiting. The patient's past medical history was not significant, with no previous cardiac history.

On presentation, the patient's vital signs were blood pressure 145/95 mmHg, heart rate 123 bpm, respiration rate 45 breaths/min, saturating 72% on room air with signs of respiratory struggle, temperature was 40˚C. On chest auscultation, there were bilateral rales audible over both lung fields. Chest x-ray showed radiological appearance in favor of extensive hypoximiant pneumonia. Her electrocardiogram (ECG) showed sinus tachycardia.

Laboratory studies disclosed the following values: white cell count 25000 /L (49% neutrophils). Blood urea and creatinine levels were normal (Blood urea was 0.24 g/L and creatinine was 9.4 mg/L) with a normal sodium level of 142 mmol/L (normal range: 135–145 mmol/L), and a normal potassium level of 4.7 mmol/L (normal range: 3.5–5.0 mmol/L). The level of C-reactive protein was raised to 250 mg / l (normal <5 mg / l).

She was diagnosed with severe pneumonia and was admitted to intensive care for intravenous ciprofloxacin treatment and clinical monitoring.

48 hours after admission, the patient had a cardiorespiratory arrest, and cardiopulmonary resuscitation (CPR) was started? The initial cardiac rhythm was treated as pulseless ventricular tachycardia.

Defibrillation resulted in sinus rhythm and spontaneous circulation and respiratory effort were restored after five minutes of CPR. Although the patient was initially drowsy, physical examination was otherwise unremarkable. Postresuscitation ECG documented a markedly increased QTc of 580 ms.

Blood taken during CPR revealed: Sodium 138 mmol/L, potassium 2.6 mmol/L, urea 1.7 g/L, creatinine 17 mg/L, glucose 0.92 g/L.

Ciprofloxacin was discontinued and replaced with cephalosporin with correction of the potassium to 4.3mmol/L. and the QTc interval normalized within three days. There were no further arrhythmias.

DISCUSSION

The basic understanding of the ionic basis of the cardiac action potential provides the foundation for explaining the pathophysiology of Acquired long QT syndrome (LQTS) and the development of torsade de pointes (TdP). Myocytes (cardiac muscle cells) are polarized in the resting state because of differences in ionic concentrations and electrical charges that normally exist across the cell membrane. The major ionic differences are the greater concentration of potassium in the intracellular fluid and the greater concentrations of sodium, calcium, and chloride in the extracellular space. The resting membrane potential (RMP) of a working myocyte is about –90 mv. Thus, the inside of the resting myocyte is negative with respect to the outside (Kunkler, K. 2002).

Myocytes continuously and synchronously undergo depolarization or excitation, and repolarization, or recovery. One cycle of depolarization and repolarization is called the cardiac action potential **(Figure 1).** Depolarization is due to the influx of the positive ions, sodium and calcium, through specific ion channels in the cell membrane of the myocyte. This influx changes the membrane potential to +30 mv. Repolarization is largely due to the efflux of potassium ions from the myocyte through specific ion channels. This returns the myocyte to RMP. During depolarization, and part of repolarization, these cells are unable to respond to another stimulus. This period of time is the effective refractory period.

During the latter part of repolarization these cells again become responsive to an electric stimulus. This period of time is called the relative refractory period.

During the relative refractory period an ectopic stimulus can initiate TdP in people with LQTS (Kunkler, K. 2002).

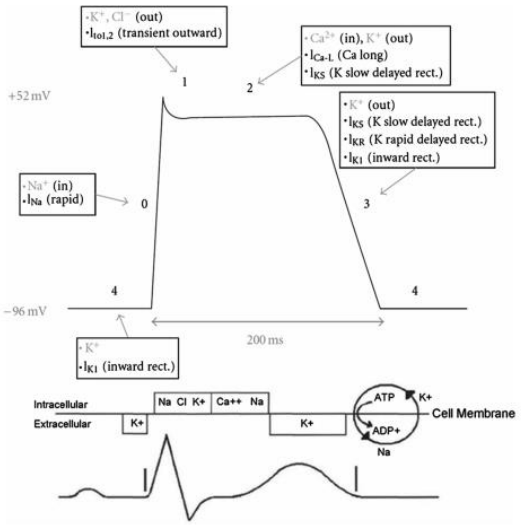

Fig 1: The cardiac action potential and its relationship to ventricular refractory periods (effective refractory period [ERP] and relative refractory period [RRP]) and the surface ECG (Kunkler, K. 2002).

Antibiotics such as the macrolide and quinolone have been associated with risk of QT prolongation and arrhythmias. Both compounds are known to prolong the cardiac action potential and to block the delayed rectifier K channel, K which is a known target for compounds K(Vr) which prolong QT interval (Patmore, L. *et al.*, 2000).

The effects of the fluoroquinolones sparfloxacin, moxifloxacin, grepafloxacin and

ciprofloxacin on the Kq channel encoded by the HERG has been reported by Bischoff *et al.*, (2000). Ciprofloxacin was found to have little interaction with the HERG channel at concentrations up to 100 ug/ml, whilst sparfloxacin, grepafloxacin and moxifloxacin inhibited HERG currents with IC values of 13, 50 37 and 41ug/ml, respectively. This rank order of potency correlates well with the functional prolongation of action potential duration observed in this study. The more modest prolongation of action potential duration by ciprofloxacin in this study is associated with a little or no block of HERG at concentrations up to 100 ug/ml (Patmore, L. *et al.*, 2000; Bischoff, U. *et al.*, 2000; Adamantidis, M. M. *et al.*, 1998 ; & Chiba, K. *et al.*, 2004).

Comparison of the concentrations at which these agents prolong action potential duration with the estimated therapeutic free plasma levels suggest that sparfloxacin may cause prolongation of action potential duration and therefore QT interval at plasma levels associated with antimicrobial efficacy. For moxifloxacin and grepafloxacin, prolongation of action potential duration and QT interval may be noted at the upper end of the plasma level range required for antibiotic activity and at a level over threefold higher. For ciprofloxacin, a wider safety window is evident with more modest but statistically significant prolongation of the action potential duration apparent at 3–10 times the anticipated therapeutic plasma level (Patmore, L. *et al.*, 2000).

The QT interval represents the duration of ventricular depolarization and repolarization (Rajendram, R. 2020; Lankipalli, R. S. *et al.*, 2005 ; & Rajendram, R. *et al.*, 2011). It is measured on the surface ECG from the beginning of the QRS complex to the end of the T wave (Rajendram, R. 2020; Lankipalli, R. S. *et al.*, 2005 ; & Rajendram, R. *et al.*, 2011).. At least 3–4 cardiac cycles should be used to derive a mean value (Rajendram, R. 2020; Lankipalli, R. S. *et al.*, 2005 ; & Rajendram, R. *et al.*, 2011).. This mean value of the measured QT interval must then be corrected for heart rate (Rajendram, R. 2020; Lankipalli, R. S. *et al.*, 2005 ; & Rajendram, R. *et al.*, 2011).. Heart rate corrected QT Intervals (QTc) > 0.44s are abnormal (Rajendram, R. 2020).

The QT interval represents the summation of the action potentials (AP) of ventricular myocytes. The AP results from the flow of ions through channels across a cell membrane. If changes in ion concentrations or myocyte channel function increase the inward current or decrease the outward current, AP duration is increased and, the QT interval is prolonged.

Prolongation of the QT interval may be congenital or acquired (Chiang, C.E. 2004). In the present illustrative case prolongation of the QT interval was caused by the low serum potassium and ciprofloxacin.

Acquired LQTS is the most common form of LQTS. The risk factors for this disorder include drugs that prolong repolarization (QT interval); electrolyte imbalance, particularly hypokalemia and hypomagnesemia; bradycardia; cardiac ischemia with reperfusion; left ventricular dysfunction; severe dieting; acute central nervous system injury; and congenital LQTS. Females are at higher risk due to their longer QT interval. The risk factors listed above can singly, or in combination, alter myocardial refractoriness, resulting in TdP. Pharmacologic agents that block potassium repolarization channels are the most common cause of acquired LQTS. Examples of these drugs are the class IA, IC, and III antiarrhythmics. Prolongation of the QT interval usually precedes TdP (Kunkler, K. 2002). Torsade de pointes in patients on antiarrhythmic therapy is often precipitated by hypokalaemia or hypomagnesaemia. So it is important to detect and treat electrolyte derangements in these patients (Kunkler, K. 2002 ; & Lankipalli, R. S. *et al.*, 2005).

Q-T prolongation as a class effect of the fluoroquinolones has been proposed; however, varying affinities of each individual agent to IKr may exist. Fluoroquinolone-induced Q-T prolongation is most commonly associated with gatifloxacin, moxifloxacin, and the withdrawn agents sparifloxacin and grepafloxacin. Reports exist of levofloxacin or ciprofloxacin-induced Q-T prolongation; however, cases reporting the involvement of ciprofloxacin are so few that its Q-T-prolonging potential is very improbable (Knorr, J. P. *et al.*, 2008). The percentage of patients taking quinolones who will experience QTc prolongation requiring discontinuation is less clear (Prabhakar, M., & Krahn, A. D. 2004).

Fluoroquinolones are bactericidal agents that directly inhibit DNA synthesis by inactivating two enzymes. They are being used with increasing frequency because of their wide spectrum of antimicrobial activity against common respiratory, gastrointestinal, and genitourinary pathogens. The case presented here illustrates ciprofloxacin's potential to cause proarrhythmia via QTc prolongation. It is interesting that multiple risk factors were present in this case. However, a clear temporal relationship existed between quinolone initiation and QT-mediated symptomatic arrhythmias. (Mitcheson, J. S. *et al.*, 2000 ; Yang, T. *et al.*, 2001 ; Roden, D. M. 2003 ; & Roden, D. M. 2000).It can be speculated that the ambient repolarization environment prior to ciprofloxacin initiation reflected reduced repolarization reserve that was potentiated by ciprofloxacin (Prabhakar, M., & Krahn, A. D. 2004).

CONCLUSION

The LQTS has emerged as an increasingly common clinical problem with potentially lethal consequences. The aging population and the practice of polypharmacy increase the risk of drug-induced LQTS. Heightened awareness of this problem has resulted in several preventive measures: genetic research intended to identify patients at risk for drug-induced arrhythmia is ongoing, and rational design of drugs devoid of undesired affects on cardiac ion channels is in progress. For the time being, it is the role of the prescribing clinician to screen for patient risk factors and environmental factors associated with LQTS and TdP before starting pharmacotherapy in any patient.

Albeit rare, ciprofloxacin must be added to the list of agents that can cause QTc prolongation and life-threatening arrhythmias, particularly when it is used in patients with other known risk factors

REFERENCES

1. Adamantidis, M. M., Dumotier, B. M., Caron, J. F., & Bordet, R. (1998). Sparfloxacin but not levofloxacin or ofloxacin prolongs cardiac repolarization in rabbit Purkinje fibers. *Fundamental & clinical pharmacology*, *12*(1), 70-76.
2. Bischoff, U., Schmidt, C., Netzer, R., & Pongs, O. (2000). Effects of fluoroquinolones on HERG currents. *European journal of pharmacology*, *406*(3), 341-343.
3. Chiang, C.E. (2004). Congenital and acquired long QT syndrome. *Current concepts and management. Cardio Rev. 12*(4), 222-34. [PMID: 15191637]
4. Chiba, K., Sugiyama, A., Hagiwara, T., Takahashi, S. I., Takasuna, K., & Hashimoto, K. (2004). In vivo experimental approach for the risk assessment of fluoroquinolone antibacterial agents-induced long QT syndrome. *European journal of pharmacology*, *486*(2), 189-200.
5. Knorr, J. P., Moshfeghi, M., & Sokoloski, M. C. (2008). Ciprofloxacin-induced QT interval prolongation. *American Journal of Health-System Pharmacy*, *65*(6), 547-551.
6. Kunkler, K. (2002). Acquired long QT syndrome: risk assessment, prudent prescribing and monitoring, and patient education. *Journal of the American Academy of Nurse Practitioners*, *14*(9), 382-389.
7. Lankipalli, R. S., Zhu, T., Guo, D., & Yan, G. X. (2005). Mechanisms underlying arrhythmogenesis in long QT syndrome. *Journal of electrocardiology*, *38*(4), 69-73.
8. Lankipalli, R. S., Zhu, T., Guo, D., & Yan, G. X. (2005). Mechanisms underlying arrhythmogenesis in long QT syndrome. *Journal of electrocardiology*, *38*(4), 69-73.
9. Mitcheson, J. S., Chen, J., Lin, M., Culberson, C., & Sanguinetti, M. C. (2000). A structural basis for drug-induced long QT syndrome. *Proceedings of the National Academy of Sciences*, *97*(22), 12329-12333.
10. Patmore, L., Fraser, S., Mair, D., & Templeton, A. (2000). Effects of sparfloxacin, grepafloxacin, moxifloxacin, and ciprofloxacin on cardiac action potential duration. *European journal of pharmacology*, *406*(3), 449-452.
11. Prabhakar, M., & Krahn, A. D. (2004). Ciprofloxacin-induced acquired long QT syndrome. *Heart Rhythm*, *1*(5), 624-626.
12. Rajendram, R. (2020). Acquired Long QT Syndrome: A Review of the Literature. *Asploro Journal of Biomedical and Clinical Case Reports*, *2020*(1), 67.
13. Rajendram, R., Ehtisham, J., & Forfar, C. (2011). *Oxford Case Histories in Cardiology*. Oxford University Press.
14. Roden, D. M. (2000). Acquired long QT syndromes and the risk of proarrhythmia. *Journal of cardiovascular electrophysiology*, *11*(8), 938-940.
15. Roden, D. M. (2003). Genetic polymorphisms, drugs, and proarrhythmia. *Journal of interventional cardiac electrophysiology*, *9*(2), 131-135.
16. Yang, T., Snyders, D., & Roden, D. M. (2001). Drug block of I Kr: model systems and relevance to human arrhythmias. *Journal of cardiovascular pharmacology*, *38*(5), 737-744.