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Case Report

A rare case of Levofloxacin induced ventricular arrhythmia

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ABSTRACT

Drug induced cardiac arrhythmias are seen commonly in clinical practice. Amongst drugs, antibiotics have a specific predisposition, and amongst them, macrolides and fluoroquinolones are specifically seen to have such a tendency. However, amongst fluoroquinolones, the rate of incidence of quinolone induced cardiac arrhythmia is reported as 5.4 cases per 10 million prescriptions. Here, we report a rare case of a probable Adverse Drug Reaction (ADR) i.e., Left Ventricular inferoposterior surface bigeminy recorded 24 hours after initiation of levofloxacin which disappeared after 24 hours of its discontinuation.

Keywords: Levofloxacin, Ventricular Bigeminy, Naranjo Score, Adverse Drug Reaction, QT prolongation

INTRODUCTION

A wide variety of drugs have been associated with cardiac arrhythmias. Many medications such as terfenadine, astemizole, have been withdrawn from circulation because of occurrence of severe rhythm disturbance endangering life. Certain classes of antibiotics are specifically known to cause such adverse reactions, such as Macrolides and Fluoroquinolones (FQ).[1] Both these groups are known to cause QT prolongation by concentration dependent action on the rapidly acting delayed rectifier potassium channel (hERG/IKr channel).[1] Risk factors for FQ induced Torsades de Pointes (TdP) include female gender, bradycardia, organic heart disease, dyselectrolytemia (especially hypokalemia, hypocalcemia and hypomagnesemia), and others.[2] Falagas ME et al concluded that the proarrhythmic potential of all FQs was not the same, with moxifloxacin having the highest, and ciprofloxacin having the lowest potential.[2] Here, we report a case of one such patient, who developed ventricular arrhythmias following Levofloxacin administration.

CASE REPORT

A 59-year-old long standing uncontrolled diabetic female (HbA1c: 11.1%) on oral hypoglycemic agents (Glimepiride, Metformin, Teneligliptin and Voglibose) and with evidence of target organ damage (diabetic retinopathy and peripheral arterial occlusive disease, status post aorto-tibial angioplasty), presented in the hospital with complaints of acute febrile illness of 4 days, associated with burning micturition and anorexia. She had a similar history of urosepsis around 2 years ago, and was managed with Injectable Piperacillin + Tazobactam at that time. On presentation, routine investigations were suggestive of acute urinary tract infection (UTI). ECG on admission was normal (Figure-1). After sending urine culture, the patient was initially started on injectable Cefoperazone + Sulbactam 3 gm twice a day. Blood glucose levels were controlled on Regular Human Insulin for the acute infective phase. However, after persistent fever spikes for nearly 48 hours, oral Levofloxacin 500 mg once a day was added. Within 24 hours of adding it (1 dose), the patient developed a regularly irregular pulse. The ECG (Figure-2) was now showing ventricular bigeminy localizing near the inferoposterior area of the Left Ventricle (LV), and no retrograde atrial activation. Corrected QT interval was 495 msec (QT interval 400 msec, Pulse: 92/min (Normal: 60-100 beats/min). As can be seen, the premature contractions were dangerously close to the normal QRS complexes, with a fixed coupling interval of only 360 msec, and a Ventricular Premature Contraction (VPC) burden of 50%. This was coexistent with mild hypomagnesemia (1.5 mg/dl) (Normal:

1.8 to 2.4 mg/dl) and mild hyponatremia (126 mmol/lit) (Normal: 136-145 mmol/lit). Serum total calcium was marginally low (7.9 mg/dl) (Normal: 8.5-10.1 mg/dl). Blood investigations during the course of hospitalization have been mentioned in Table-1. Levofloxacin induced ventricular arrhythmia was suspected, and the drug was discontinued. Urine cultures showed E. coli, susceptible to Cefoperazone + Sulbactam, which was continued. She responded well after 60 hours, and no further fever spikes were noted. Serial ECG monitoring done 12 hourly, showed occasional VPC's from the same site (Figure-3). 24 hours after discontinuation of Levofloxacin, the ECG once again reverted to normal sinus rhythm (Figure-4). The patient was discharged on oral cefixime + clavulanate, as per the culture reports, and other supportive medications.

Table-1: Investigations during the course of hospitalization

	On admission	Day 3 of admission (On the day of starting of Levofloxacin)	Day 5 of admission (24 hours after discontinuation of Levofloxacin)
Total Leucocyte Count (x1000/µL)	17.3	13.5	8.3
Differential Counts (N/L/E/M) (in %)	88/10/01/03	76/19/01/04	68/23/01/08
C-Reactive Protein (in mg/dl)	118.3	228.5	93.4
Creatinine (in mg/dl)	1.46	1.42	1.12
S. Sodium (mmol/L)	126	130	126
S. Potassium (mmol/L)	4.9	4.2	4.2
S. Magnesium (mmol/L)			1.5
S. Total Calcium (mg/dl)		7.9	
Corrected S. Total Calcium (in mg/dl)		8.5	
S. Ionized Calcium (mmol/L)		1.19	
Urine Routine and Micro	4-6 pus cells / hpf		
Total Bilirubin / Direct Bilirubin / Indirect Bilirubin (mg/dl)	0.6 / 0.2 / 0.4		
Albumin (gm/dl)	3.3		
ALT / AST (in U/L)	11/10		

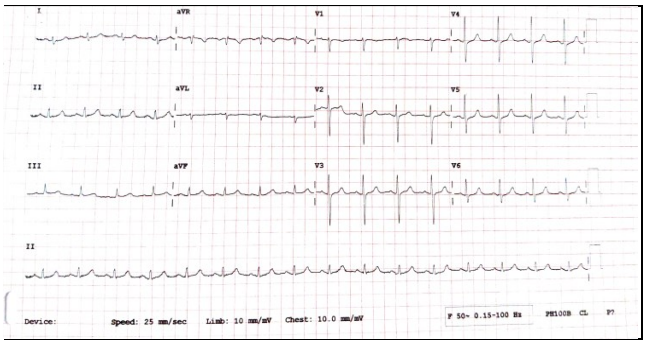

Figure-1: ECG on admission showing Normal Sinus Rhythm (NSR)

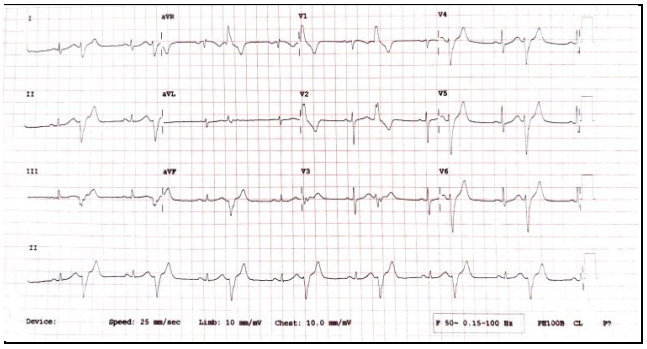

Figure-2: ECG after 24 hours of Levofloxacin administration, showing Ventricular bigeminy from Inferoposterior region of LV

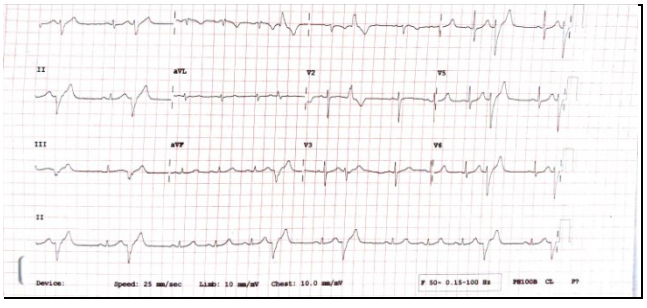

Figure-3: ECG after 12 hours of discontinuation of Levofloxacin, showing occasional VPCs

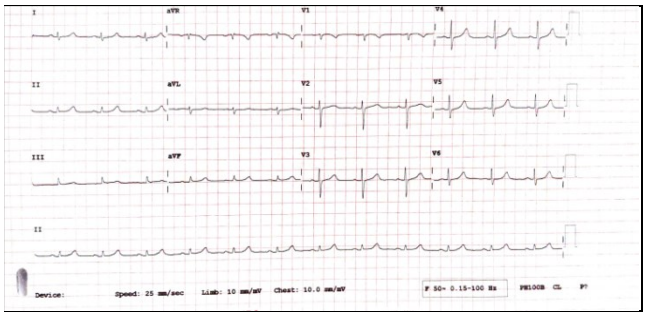

Figure-4: ECG after 24 hours of discontinuation of Levofloxacin

DISCUSSION

FQs have been shown to affect the corrected QT interval (QTc). However, this is more common with ciprofloxacin, moxifloxacin and gatifloxacin.[1,2] Ventricular arrhythmias, secondary to levofloxacin administration, is not routinely observed. Tsikouris et al[3] and Makaryus et al[4] found no effect of oral Levofloxacin 500 mg once a day on QTc, neither were episodes of TdP noted. Noel et al[5] evaluated the doses of oral levofloxacin that could lead to a statistically significant prolongation of the QTc. They found that in patients of UTI, oral Levofloxacin 500 mg once a day did not affect the QTc interval. However, single dose of 1000 mg led to a statistically significant prolongation of the QTc (from 1.5 msec to 3.9 msec) after 24 hours. Similarly, a single dose of 1500 mg also had the same effect on the QTc (from 6.4 msec to 7.7 msec) after 24 hours. This was in accordance to a study by Noel et al[6] who found a similar increase in the QTc after single doses of 1000 mg (from 3.5 msec to 4.9 msec). As concluded by Rao GA et al,[7] levofloxacin caused a statistically significant rise in cardiac mortality and arrhythmias over a 10 days prescription. The most frequent duration of treatment for levofloxacin, as per Rao GA et al[7] ranged from 3 to 14 days. However, the current case is, to the best of the knowledge of the authors, is the first to report a ventricular arrhythmia secondary to Levofloxacin 500 mg, single dose.

In the present case, the patient was administered oral Levofloxacin 500 mg. Following which, the patient developed LV bigeminy rhythm within 24 hours. For causal assessment, the Naranjo Score[8] was calculated, which came to 7, suggesting probable Adverse Drug Reaction (ADR). This could likely be an idiosyncratic reaction, since no such cases have been reported where a single dose of parenteral levofloxacin led to a rhythm disturbance, along with the prolongation of the QTc. However, since the fluoroquinolones act via the hERG/IKr channel, a detailed pharmacological study may be required to establish a causal association. A repeat documentation of ventricular bigeminy with QTc prolongation, if obtained, could raise the Naranjo score to 9, making it a definite ADR. However, this was not attempted due to ethical reasons. Risk factors for this patient, were female gender and minimal hypomagnesemia with normokalemia. The patient did not require any intervention for the ADR, and withdrawal of the drug led to reversal of the ECG findings. However, it must be noted, that routine low dose oral Levofloxacin could also lead to arrhythmias, in a certain predisposed population.

CONCLUSIONS

Irrespective of the dose, medications that can predispose a patient to cardiac arrhythmias must be used with caution, if not with fear, especially in patients with concomitant risk factors. Although Levofloxacin is less commonly associated with such ADR's, a watch must be kept for the occurrence of such rare possible ADR's.

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