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Clarithromycin Induced Digoxin Toxicity: Case Report and Review

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With the advent of newer broader spectrum macrolides, a rapid surge in their use has been noticed in Pakistan. Interaction between macrolide antibiotics and other commonly used medications can be life threatening. We report a case of clarithromycin interaction with warfarin and digoxin leading to digoxin toxicity.

Case Report

A 56 year-old woman with history of severe rheumatic mitral stenosis and atrial fibrillation, was being treated with digoxin 0.25mg and warfarin 3mg daily for the past five years. Patient's target international normalized ratio (INR) was being maintained between 2.0 and 3.0. She presented to our institution with fever and cough for 5 days. Two days prior to presentation, she was started empirically on clarithromycin 500 mg twice daily by her primary care physician for presumed community acquired pneumonia. Her chest X-ray on admission was abnormal for left lower lobe pneumonia. Patient was started on intravenous ampicillin/clavulanic acid 1.2 gm every eight hours and clarithromycin was also continued. Initial electrocardiogram (EKG) showed atrial fibrillation with ventricular rate of 70/minute with minor lateral T wave abnormalities (Figure 1).

Two days later patient developed profound weakness associated with nausea, vomiting, dizziness and dyspnea. On examination pulse rate was 40/minute. Another 12 lead EKG done showed underlying atrial fibrillation with complete heart block, junctional escape rhythm and multifocal PVCs with fixed coupling interval (Figure 2). Laboratory results revealed digoxin level of 8.7 ng/ml (therapeutic range=1.0-2.6) and an international normalized ratio (INR) of 3.97 (2.0-3.0). Patient was shifted to coronary care unit and all medications were discontinued except ampicillin/clavulanic acid. Due to nonavailability of digoxin binding fragments only a temporary pacemaker was inserted to increase the heart rate. Her heart rhythm returned to baseline (atrial fibrillation) after 48 hours with decrease in digoxin level to 3.0 ng/ml. The patient was finally discharged on day 7 with a digoxin level 1.6 ng/ml and a plan to undergo mitral valve replacement.

Discussion

Interaction between macrolide antibiotics and other commonly used medications is now a frequent occurrence. One of the most likely explanations is the property of macrolide antibiotics, especially erythromycin, to inhibit

cytochrome CYP450 hepatic microsomal enzyme system, particularly CYP1A2 and CYP3A4 isoenzymes.¹⁻³ Introduction of newer macrolides with structural modifications resulted in compounds with not only varying antibacterial activity but also variability in their potential for interactions with other drugs.⁴ Many of the macrolides are metabolized by CYP3A4 to metabolites which form complexes with heme (iron) molecules of the cytochrome, causing CYP3A4 to lose its catalytic ability resulting in elevated serum levels of drugs cleared by the hepatic CYP450 oxidizing system.^{5,6}

Ten percent of population on chronic digoxin therapy convert upto 40% of ingested digoxin to inactive digoxin reduction products (DRPs) due to action of *Eubacterium lentum*, an anaerobic bacillus which is part of normal gut flora. It has been suggested that macrolide antibiotics, especially erythromycin and possibly clarithromycin alter the gut flora by decreasing *Eubacterium Lentum* in the gut, thereby reducing the conversion of digoxin to DRPs⁶⁻⁸ and thus increasing serum digoxin level leading to toxic effects and increased morbidity.

To our knowledge, there have been case reports of clarithromycin induced digoxin toxicity but only one report of clarithromycin induced digoxin toxicity and concomitant warfarin interaction.^{6,9,10} Increased digoxin levels secondary to concomitant administration of erythromycin or clarithromycin presumably occurred due to inhibition of *Eubacterium lentum* within the gut flora, which is now known to be principally responsible for the conversion of digoxin to DRPs in the gut, leading to increased serum digoxin level as described above.^{6,7,11} Another possible mechanism of clarithromycin and digoxin interaction is reduction of renal excretion of digoxin. It is suggested that P-glycoprotein plays an important role in the renal secretion of digoxin, and that clarithromycin can decrease renal digoxin excretion by inhibiting P-glycoprotein-mediated transport.¹² Digoxin toxicity was reported 3-17 days after the institution of clarithromycin (8.1 ± 4.8 day, $n = 9$). The wide variation in the time required for the appearance of toxicity may imply the different mechanisms involved in each case.¹³

The macrolide antibiotics, also interact with the commonly prescribed anticoagulant warfarin, which, among other drugs is metabolized by the CYP450 system with predominant involvement of CYP3A4.^{4,6} As the therapeutic range of warfarin is narrow, warfarin treatment needs to be monitored carefully with dose reduction when concomitant treatment with macrolides is instituted.

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In this case we have described potential drug interaction between clarithromycin, digoxin and warfarin. Patient mentioned in this case was maintaining her INR between the desired range of 2.0-3.0 without any problem on 3mg/day of warfarin. After four days of therapy with clarithromycin, she developed life threatening complete heart block secondary to elevated levels of digoxin and an INR beyond therapeutic range which increased her risk of hemorrhage. There has been a case reported which described similar interactions between these three drugs.⁶

Almost all antibiotics can potentiate the effects of warfarin by inhibiting its hepatic metabolism. Erythromycin-warfarin interaction has shown that erythromycin can markedly elevate the prothrombin time by inhibition of CYP450 system.^{4,6} Erythromycin and troleandomycin have the highest affinity for CYP3A4 isoenzyme and therefore the strongest ability to inhibit substrate breakdown. Clarithromycin has a lower affinity for cytochrome system, leading to less significant interactions with substrates of CYP3A4.⁷ Since clarithromycin potentiates the effect of warfarin, careful monitoring of INR is warranted. Two case reports suggest that like erythromycin, clarithromycin, by inhibiting hepatic cytochrome system, can lead to potential-

ly high risk of hemorrhage by increasing the serum warfarin level.^{3,6}

Patient presented had been compliant with the prescribed doses of digoxin and warfarin for years without any problems. Introduction of clarithromycin to her regimen exposed her to serious adverse drug interactions between these drugs with the development of life threatening complete heart block and increased INR with potential risk of hemorrhage. Therefore we highlight serious drug interactions of commonly prescribed antibiotics in patients on long term digoxin and warfarin therapy.

In this case we have described potential interactions between drugs commonly used in clinical practice with the development of life threatening adverse reactions. This case gives a better perspective of the adverse drug interactions which can occur in patients on long term digoxin and warfarin with introduction of macrolide antibiotic, clarithromycin. Prescribing physicians should be aware of possible drug interactions when starting a new drug in patients on chronic drug therapy, thus preventing prolonged unnecessary hospitalizations and life threatening complications.

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