Vol 9| Issue 1| 2019 | 12-14.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research
www.ijcpcr.com

EFFECTS OF CLARITHROMYCIN ON CARDIOVASCULAR SYSTEM – A REVIEW

K.Ramachandran[1]* & Bishnu Regmi[2]

Lecturer and Chief of Hospital Pharmacist, Department of Pharmacy, College of Medical Sciences, Bharatpur 10, Chitwan District, Nepal.
[2]Regional Pharmacovigilance center, Department of Pharmacy, College of Medical Sciences -Teaching Hospital, Bharatpur 10, Chitwan District, Nepal.

ABSTRACT
Clarithromycin is available in the form of oral use dosage formulation which is a semi-synthetic antimicrobial. This widely reported side effects/adverse effects of macrolides include abdominal pain, severe skin reactions, GI related helath issues, vomiting and diarrhea. The present review explained the side effects, mode of action, therapeutic uses and brief notes on Clarithromycin.

Key words: Clarithromycin, antimicrobial, side effects.

INTRODUCTION

Clarithromycin is available in the form of oral use dosage formulation which is a semi-synthetic antimicrobial. This semi-synthetic drug appears in white to semi-white colour with a crystalline powder appearance. Coming to solubility of clarithromycin, it is slightly soluble in methanol, acetonitrile, and ethanol and clarithrmycin is practically insoluble in water [1]. Macrolides, that are mostly preferred are clarithromycin, roxithromycin, erythromycin, and azithromycin. The widely reported side effects/adverse effects of macrolides include abdominal pain, severe skin reactions, GI related helath issues, vomiting and diarrhea[2].

As presented priorly, it is a semi-synthetic macrolide with 14-membered ring in it. In susceptible organisms, the inhibition of RNA-dependent protein synthesis is brought by binding of clarithromycin in the 50S ribosomal subunit by clarithroycin. Due to presumed eradication of tumerorigenic Helicobacter pylori infection, clarithromycin also eradicates lymphomas of gastric Mucosa-Associated Lymphoid Tissue (MALT). It also possibly inhibits angiogenesis by acting as a biological response modulator, thereby, also inhibits the tumor growth by altering the tumor growth expression [3].

Clarithromycin acts synergistically with its parent compound by getting metabolized to 14-OH clarithromycin. Clarithromycin reversibly binds to the domain V of the 23S ribosomal RNA of 50S subunit by penetrating into the bacterial cell wall, and also blocks the translocation of aminoacyl transfer-RNA therby, inhibits the polypeptide synthesis. Drug efflux pupmp which is energy dependent and CYP3A4 isoenzyme of the hepatic microsomes are inhibited by clarithromycin[4,5].

Toxicity of clarithromycin may lead to various clinical conditions like abnormal taste, abdominal discomfort, dyspepsia, nausea and diarrhea. Transient hearing has also been reported in high dose users of clarithromycin. A type of colitis namely Pseudomembraneous colitis has also been reported by use of clarithromycin. Mild allergic/sensitivity reactions ranging from skin eruptions, utricaria to Stevens-Johnson syndrome have been reported. Severe hepatic dysfunctions have also been reported very rarely in some cases. Though hepatic failure is reversible in most of the cases, fatalities from hepatic failure have also been reported. Some reversible side effects by using clarithromycin includes, decolouration of tooth which can be reversed by dental

Corresponding Author :- **K.Ramachandran** Email:- rcrama911@gmail.com

cleaning. During animal studies with clarithromycin, the fetal abnormalities like cleft palate, fetal growth retardation and cardiovascular defects have been reported. QT prolongation may also be seen n some cases [6].

Erythromycin and clarithromycin are similar in their pharmacokinetic properties to large extent. Clarithrmycin is the macrolide that is presented with greatest bio-availability by its rapid absorption from the gastrointestinal tract [7]. Pharmacokinetically clarithromycin represents linear PK and attains steady-state concentration in 3-4days from the startup of use [8]. In patients with history of pulmonary hypertension, pulmonale, transaminitis, and hypoalbuminemia the use of clarithromycin resulted in arrhythmias. In patients with history of hepatitis C and heart failure and on clinical procedure of dialysis, were are reported with arrhythmias by use of clarithromycin[9].

By inhibiting the activity of potassium ion channel of hERG (***human Ether-a-go-go Related Gene***) the clarithromycin acquired QT syndrome and TdP and also by the rapid rectifier of K^+ current, I_{Kr}[10,11]. During the animal studies of clarithromycin in rabbits, it was observed that on concentration-dependent fashion at a dose ranging from 3 to 100 µM, the native I_{Kr} amplitude and APD (Action Potential Duration) was prolonged in cardiac tissues[12]. By rapidly activating the delayed rectifier potassium current I_{Kr} which are present in the cardiac myocytes, the QT interval is prolonged by clarithromycin [13], which plays an important role in cardiac repolarization [14].

Antiarrhythmics, promotility medications, antipsyhotics and antimicrobials are the common drugs which may cause prolongation of QT interval in patients, which are named as drug-induced QT prolongation. Genetic predisposition, cardiac complications, female gender, old age are the predisposing factors for developing long QT interval. Development of ***torsades de pointes*** (TdP) is seen due to QT interval prolongation, which may result in sudden cardiac deaths [15]. Due to the above reported effects of clarithromycin in cardiac patients, the USFDA (United Nations Food and Drug Administration) has suggested to advise caution in clarithromycin prescribing for cardiac patients in particular, which is available by the brand name Biaxin. Hereby, preventing the future cardiac deaths due to clarithromycin[16].

Even patients with normal QT interval may also develop prolonged cQT interval due to clarithromycin which is noted from the above mentioned effects of the drug[17]. Other antibiotics like amoxicillin and ciprofloxacin can be replaced by clarithromycin if the antibiotic use is required for long period of time. Thus, clarithromycin should be taken for PV (pharmacovigilence) studies and monitoring drug interactions. In addition to the PV studies, it is better recommended for multi-centric large scale population studies to exactly evaluate the clinical impact of the drug, in comparison to the large scale use of other antibiotics like azithromycin and others. Therefore the health care professionals should over weigh the risk and benefit ratio of clarithromycin before prescribing the drug even in cases required with short term use of antibiotics.

REFERENCES

1. Winkel P, Hilden J, Hansen JF, Kastrup J, Kolmos HJ, Kjoller E, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10 years in the CLARICOR randomised, blinded clinical trial. *Int J Cardiol*,182, 2015, 459-65.
2. RC Baselt. 9th Edition. USA: Biomedical Publications; 2011. Disposition of toxic drugs and chemicals in man.
3. Clarithromycin: Available at. https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary= NCI_Thesaurus&ns=ncit&code= C1054**.**
4. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H: Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet.* 369(9560), 2007, 482-90.
5. Zuckerman JM, Qamar F, Bono BR. Macrolides, ketolides, and glycylcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. Infect Dis Clin North Am. 23(4), 2009, 997-1026.
6. Piscitelli SC, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. *Clin Pharm*., 11(2), 1992, 137-52.
7. McConnell S, Amsden G. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. *Pharmacotherapy*, 19, 1999, 404–415.
8. Abbott Laboratories (2013) Biaxin® Filmtab® (Clarithromycin Tablets, USP), Biaxin® XL Filmtab® (Clarithromycin Extended-Release Tablets), Biaxin® Granules (Clarithromycin for Oral Suspension, Usp) Package Insert. Available at: http://www.rxabbvie.com/pdf/biapi.pdf.
9. Lee KL, Jim M-H, Tang SC, Tai Y-T. QT prolongation and Torsades de Pointes associated with clarithromycin. *Am J Med*,104, 1998, 395–396.
10. Finlayson K., Witchel H., McCulloch J., Sharkey J. Acquired QT interval prolongation and hERG: implications for drug discovery and development. *Eur J Pharmacol*, 500, 2004, 129–142.

11. Abbott G., Sesti F., Splawski I., Buck M., Lehmann M., Timothy K., et al. (1999) MiRP1 forms I_{KR}potassium channels with hERG and is associated with cardiac arrhythmia. *Cell*, 97, 1999, 175–187.
12. Gluais P, Bastide M, Caron J, Adamantidis M. Comparative effects of clarithromycin on action potential and ionic currents from rabbit isolated atrial and ventricular myocytes. *J CardiovascPharmacol*, 41, 2003, 506–517.
13. Volberg WA, Koci BJ, Su W *et al*. Blockade of human cardiac potassium channel human ether-a-go-go-related gene (HERG) by macrolide antibiotics. *J. Pharmacol. Exp. Ther*. 302(1), 2002, 320–327.
14. Owen RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin.Infec.Dis*. 43, 2006, 1603–1611.
15. Paulussen AD, Aerssens J. Risk factors for drug-induced long-QT syndrome. *Neth. Heart J*. 13(2), 2005, 47–56.
16. FDA Drug Safety Communication: FDA review finds additional data supports the potential for increased long-term risks with antibiotic clarithromycin (Biaxin) in patients with heart disease 2/22/2018.
17. Mecnun Cetin, MunevverYıldırımer, SerkanOzen. Clarithromycin-Induced Long QT Syndrome: A Case Report. Case Reports in Medicine. 2012, Article ID 634652, 2.