Review

Clinical update: Macrolides and cardiovascular death

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Macrolides are one of the classes of antibiotics most commonly prescribed for sinusitis and respiratory tract infections in the urgent care and primary care setting. In particular, azithromycin tends to be a popular choice among medical providers. In May 2012, the New England Journal of Medicine published an article with findings which indicate a small increase in cardiovascular deaths that appeared to be more pronounced among patients with a higher baseline risk of cardiovascular disease. However, in May 2013, the same journal published an article that presented results showing that there was no increased risk of death due to cardiovascular causes in the general population associated with use of azithromycin. In addition, other research has reported increases in cardiovascular deaths with the use of clarithromycin and erythromycin. Unfortunately, the result is much confusion for patients and medical providers. This clinical update will review the existing data in an attempt to provide clarity for medical providers and elucidate the pros and cons of prescribing macrolides in the urgent care setting.

Key words: Macrolides, cardiovascular, antibiotics, patients, clinical update.

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INTRODUCTION

Currently there are six Food and Drug Association (FDA)-approved macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, and telithromycin. The macrolides are bacteriostatic and inhibit susceptible pathogens by binding to the bacterial 50s ribosome (Drug Points System, 2013). This effectively prevents the 50s ribosomal subunit from interacting with the 30s ribosomal subunit-tRNA-mRNA-complex; collectively called the initiation complex (Figure 1). Preventing the union of the 50s ribosomal subunit with the initiation complex inhibits the process of nucleotide chain movement of the mRNA, inhibits translocation and elongation of the amino acid chain, and consequently thwarts the translation of proteins in that cell. This ultimately results in a decrease in protein production in the bacterial cell.

The FDA has issued a warning to the public on the use of azithromycin, stating that it can cause abnormal changes in the electrical activity of the heart which can result in irregular heart rhythms and can potentially be fatal (FDA Drug Safety Communication, 2013). All of the macrolides have the listed warning that they have a risk of causing QT-interval prolongation and the ventricular

arrhythmia *torsades de pointes*. Based on a systematic review, it was found that erythromycin carries the greatest risk of QT-interval prolongation and *torsades de pointes*, followed by clarithromycin, and then azithromycin (Guo et al., 2010). However, we must bear in mind that old age, preexisting cardiac risk factors, high dose, and rapid administration are additional factors that bear significance.

Some reports about the drugs in the macrolide class propose an association with cardiovascular mortality:

(a) In 2004, it was reported that concurrent use of erythromycin and strong inhibitors of CYP3A (for example, antifungal agents, diltiazem, and verapamil) were associated with an increased risk of sudden death from cardiovascular causes and that the combination of these drugs should be avoided (Ray et al., 2004).
(b) In 2012, an observational study that involved Tennessee Medicaid patients, an association was seen between use of azithromycin and increased risk of cardiac-related mortality and it was increased in patients with pre-existing cardiovascular issues (Ray et al., 2012). This risk appeared to be more profound during the first 5
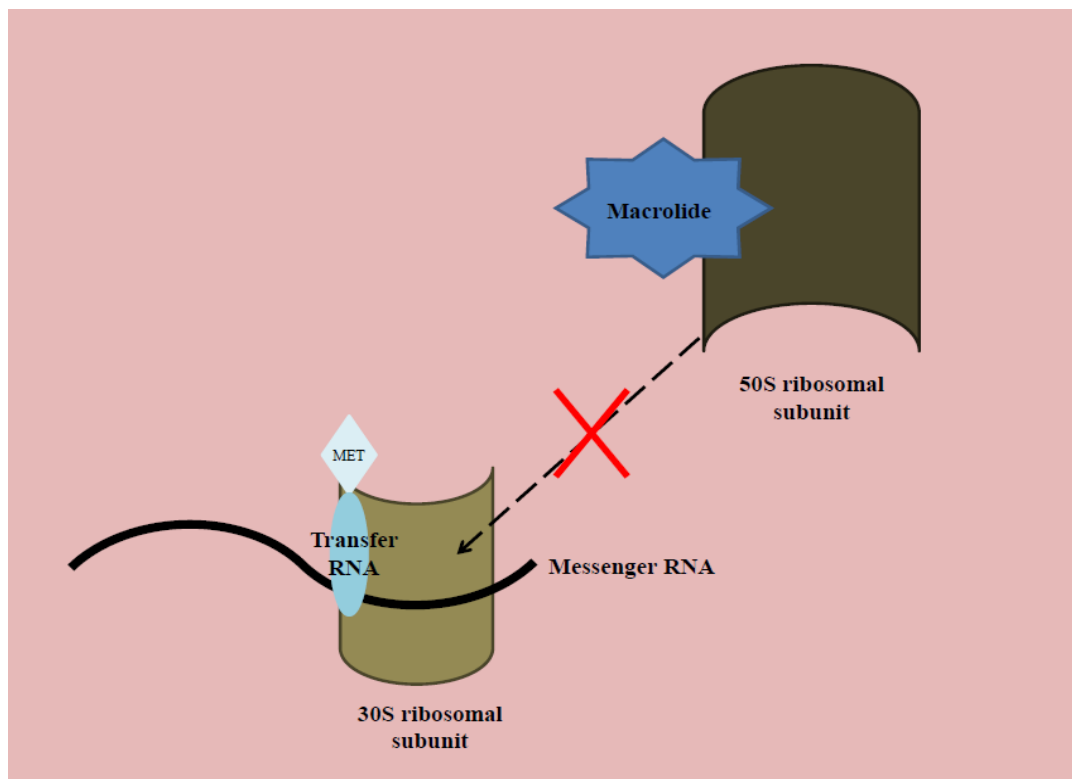
Figure 1. The initiation complex consists of mRNA bound to the bacterial 30s ribosomal subunit, which are held together by initiation factors and tRNA with the methionine start codon attached to the p-site. Under normal circumstances, the bacterial 50s ribosomal subunit binds with the initiation complex. However, when the macrolide molecule binds to the 50s subunit, the subunit is rendered unable to interact with the initiation complex and the translation of the mRNA is unable to be performed. Consequently, protein products cannot be produced by the bacterial cell.

days of treatment.

(c) In 2013, it was reported that the administration of clarithromycin for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD) or community-acquired pneumonia might be associated with an increase in cardiovascular events (Schembri et al., 2013). A significant finding in this study was that the association with increased cardiovascular events appeared last beyond the duration of the course of the drug.

The mechanism of action of the macrolide antibiotics that may be responsible for the adverse effects on the cardiovascular system remains elusive, but it is thought that these drugs cause a disruption in the electrical activity in the heart. A study in 2011 seemed to support, at least in the case of clarithromycin, that there is activation of macrophages that initiates an inflammatory cascade and, as a consequence, vulnerable plaques form over time (Winkel et al., 2011). Of course the plaque formation can increase risk of acute coronary syndromes or sudden cardiac death due to plaque rupture. Interestingly, the plaque formation theory finds further support in the fact that the Winkel et al. (2011) study

noted that the excess of mortality due to cardiovascular-related death in the clarithromycin-taking group was more profound in the group that was not on a statin when compared to the group that was taking a statin (Winkel et al., 2011).

CARDIOVASCULAR RISKS ASSOCIATED WITH AZITHROMYCIN

The drug azithromycin and the proposed cardiovascular risks have recently captured the attention of the media, which has caused some concern and even panic among patients in general. This was generated by the findings from the Ray et al. 2012 study, which was a nonrandomized observational study that involved an isolated population of Tennessee Medicaid patients (Ray et al., 2012). The findings projected a small absolute increase in cardiovascular deaths during a 5-day course of azithromycin (347,795 prescriptions) when compared to amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), and levofloxacin (193,906 prescriptions).

Statistically speaking, azithromycin demonstrated 85.2

cardiovascular deaths per 1 million courses (0.0000852%) when compared with amoxicillin with 31.5 cardiovascular deaths per 1 million courses (0.0000315%). Both increases are statistically insignificant when compared to the 29.8 cardiovascular deaths per 1 million (0.0000298%) seen in the non- antibiotic-taking group. The rate of cardiovascular deaths was higher in the patients with pre-existing cardiovascular disease who took azithromycin with 245 cardiovascular deaths per 1 million courses (0.000245%) (Ray et al., 2012). However, in relative terms, these results could be deemed statistically insignificant because this study cannot differentiate whether the cardiovascular death were due to the drug or something else, for example, lifestyle.

Significant limitations have been acknowledged in the study by Ray et al. (2012). First, because this was a nonrandomized clinical study, it cannot be excluded that the patients who received the drug under evaluation (in this case, azithromycin) differed from the control patients in some significant and undetected fashion (Mosholder et al., 2013) that could cause bias in the results. Secondly, these results were not replicated in a subsequent study. Finally, this study was performed on a relatively isolated population.

Interestingly, the Ray et al. (2012) study indicated that the perceived risk of cardiovascular mortality was significant on only days 1 to 5 (which reflects the typical 5-day duration of the Z-pak) and was no longer detected on days 6 through 10 (Ray et al., 2012).

This finding is in contrast to the findings of Schembri et al. (2013) on clarithromycin, which is in the same pharmacological class. In the Schembri et al. (2013) study, the risk of cardiovascular mortality appeared to persist long after clarithromycin was discontinued. That could also indicate two different mechanisms of action by the macrolides that potentially lead to adverse effects on the cardiovascular system. However, a specific mechanism of action has yet to be identified for either of these two drugs.

A recent study conducted by the Department of Epidemiology Research, Statens Serum Institute, at Copenhagen, Denmark found no difference in the 5-day risk of cardiovascular deaths when comparing azithromycin with penicillin V in a general population of young and middle-aged adults (Svanstrom, 2013). The patients in the Danish population had better cardiovascular health than the Tennessee Medicaid population. However, a subpopulation of the Denmark study with a history of cardiovascular disease demonstrated a slight increase in risk ratio (although it was deemed not statistically significant) for azithromycin versus penicillin V. This would be consistent with the relatively small increase seen in the risk that was projected in the Ray et al. (2012) study in those patients with pre-existing cardiovascular disease taking azithromycin.

Finally, because only an infinitesimal portion of the subjects in the studies mentioned here experienced cardiovascular associated mortality (significantly less than 1%), it would be reasonable to purpose an aberrant genetic mechanism as a potential underlying source of cardiotoxicity with the use of macrolides. This proposal may justify genome-wide analysis studies to be performed retroactively.

MACROLIDES: TO USE OR NOT TO USE?

Given these studies, medical providers are left at a peculiar juncture as to whether to change their prescribing behavior in regards to macrolides in the clinical setting. It is obvious that the gravity of any proposed drug-related cardiovascular risks must be weighed against the possible clinical benefits.

Macrolides have demonstrated advantages over other classes of antibiotics for treating certain types of infections. For example, azithromycin is the drug of choice for treatment of chlamydia infections (in conjunction with rocephin for treatment of gonorrhea). In addition, a recent study on outpatients with community-acquired pneumonia demonstrated that treatment with a fluoroquinolone or a macrolide was associated with a reduction in mortality when compared to the other classes of antibiotics (Asadi et al., 2012). In that study, it was further stratified that there was a significantly lower 30-day mortality rate in the group receiving a macrolide versus the group receiving a fluoroquinolone. When comparing these two classes of antibiotics, it is important to consider that a recent population-based study involving 605,127 subjects found an association between elevated risk of serious arrhythmia (defined as ventricular arrhythmia or sudden death) and use of the fluoroquinolones-moxifloxacin, ciprofloxacin, and gatifloxacin (Lapi et al., 2012). The greatest risk of serious arrhythmia out of the three antibiotics was seen with the use of gatifloxacin. Consequently, there are good reasons for using macrolides for conditions such as chronic sinusitis, chronic bronchitis, other COPD exacerbations, and pneumonia.

Macrolides have advantages for treatment of many ailments but given recent studies that have demonstrated an exceedingly small (and highly publicized) increase in cardiotoxicity with these drugs, medical providers need to take a few things into consideration before prescribing azithromycin, clarithromycin, or erythromycin. Macrolides should be avoided in patients with:

1. Known QT-interval prolongation or bradycardia: If a patient's past medical history is unknown, an EKG may be justified, especially for a patient who presents with signs and symptoms of QT-interval prolongation such as

Table 1. The SAME Questions for use of Macrolides.

Symbol	Parameter	Question
S	Signs/symptoms/conditions	Does the patient have signs, symptoms, or conditions that require further evaluation with an EKG or blood work?
A	Antiarrhythmics	Is the patient taking antiarrhythmics?
M	Medications	Is the patient taking medications that can cause QT-interval prolongation or bradycardia?
E	Existing cardiovascular issues	Has the patient be diagnosed with cardiovascular issues?

lightheadedness, heart palpitations, irregular heartbeat, weakness, or blurry vision. A low pulse (<60 beats per minute) should generate similar concern.

2. Metabolic conditions hypokalemia and hypomagnesemia: For such patients, prompt blood work may be in order, particularly for those who present with signs and symptoms of hypokalemia or hypomagnesemia, such as weakness, fatigue, muscle cramps, constipation, increased irritability with tremors, athetosis (repetitive involuntary movements- most noticeable within the hands), nystagmus, confusion/disorientation, depression, and alcohol abuse.

3. The use of certain antiarrhythmic agents such as:

a. Class IA- disopyramide, quinidine, or procainamide.
b. Class III- amiodarone, sotalol, ibutilide, or dofetilide.

4. Use of other drugs that can cause prolongation of the QT-interval: Tricyclic antidepressants, trazodone, fluoroquinolones, anti-malarials, ondansetron (and other anti-nausea/vomiting medications), antipsychotics, citalopram, vardenafil, cyclobenzaprine, and methadone.

Patients who have none of the conditions listed above still may have additional factors that place them in the gray area for use of macrolides. Therefore, macrolides should be used with caution in patients with:

1. A pre-existing cardiovascular condition.
2. Old age.
3. Chronic kidney disease.
4. Diarrhea or excessive use of laxatives.
5. Excessive sweating.
6. Vomiting.
7. Primary aldosteronism.
8. COPD/asthma/pneumonia and a history of frequent hospitalizations.
9. Concomitant use of CYP3A inhibitors- especially if considering the use of erythromycin.

In the presence of any of these conditions or symptoms, and the inability to use another appropriate class of antibiotics (typically due to documented allergic or adverse drug reactions), further blood work may be required prior to any urgent care or primary care provider making the decision to prescribe a macrolide.

CONCLUSION

Are macrolides dangerous? No. However, they should be avoided in patients with certain medical conditions because of the very small chance of cardiovascular exacerbations or cardiovascular death. Henceforth, any medical provider in the urgent care setting should ask himself or herself the following SAME questions list in Table 1 before prescribing a macrolide. If other antibiotic options are not feasible given the most likely diagnosis and macrolides are an only (or the best) option in a patient with clinical risk factors, then take a second to discuss with the patient the very small potential for increased cardiovascular risk associated with macrolides, ask yourself the SAME questions, and document all of this in the patient's records.

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